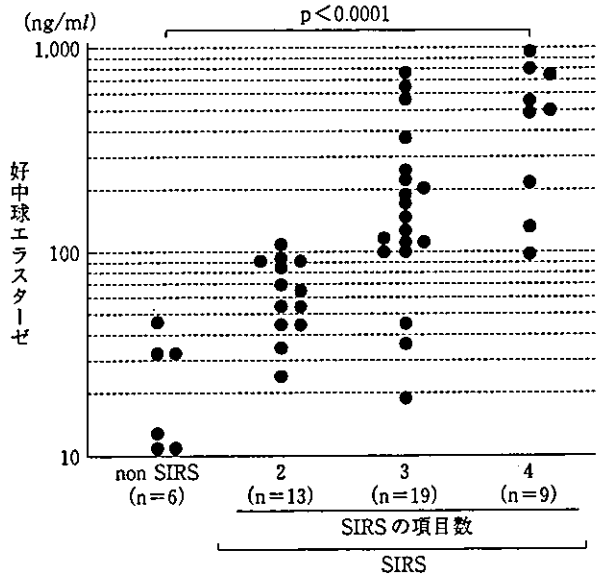

図4 SIRS項目数と好中球エラスターゼ値[10]

DR発現がよく相関し，短時間に結果が得られるため臨床的に有用であるとの報告もあるが，flow cytometerという高価な機器を用いて，採血後すぐに解析する必要があるため，利用できる施設は限られるであろう[13]．

III. サイトカインによる重症度評価

各種サイトカインの中でも，SIRS項目の異常を誘導する作用はTNF-αやIL-1が最も強く，PGE_2の産生を介して発熱や低体温，頻脈，多呼吸を誘発する．また好中球に関しては，直接血管内皮細胞への接着能を亢進して初期の白血球減少を生じさせる一方で，IL-8やG-CSFの産生を介してその後の白血球増多症へも寄与している．一方，IL-6には，直接SIRS項目の異常を惹起する作用はないが，TNF-α，IL-1および細菌内毒素などにより産生が誘導され，血中濃度が侵襲後速やかに上昇し，かつ持続するため，各種臨床試験などで重症度評価によく用いられる．

血中IL-6値は小手術では極めて低いが，侵襲の大きな手術では高値を示すなど，手術侵襲ともよく相関する．非感染性SIRSが多い外傷においてもIL-6は重症度を表すinjury severity score(ISS)と相関する．感染やショック，再手術などの侵襲が加わり，侵襲が持続，遷延化するとIL-6の高値持続や再上昇がみられ，北村らはSIRS発症3日後にIL-6>800 pg/mlの患者が，MODSに移行する可能性が高いとしている[5]．このようにIL-6は生体への侵襲度を比較的よく反映するものの，少なくとも我が国では簡便に測定できず，臨床応用に至っていないのが現状である．

おわりに

集中治療を要する患者の多くは一過性に過剰炎症状態となり，SIRS基準を満たす場合が多く，SIRS基準によって重症度，すなわちMODS発症率，予後を評価するにはかぎりがある．日常の患者管理に際し，治療追加や変更の必要性を見極めるために，患者の重症度を常に把握している必要があり，実際多くの臨床医は，無意識のうちにこれを行っているのかもしれない．しかし，病態が増悪しつつある患者を早期に発見し適切に対応するためには，本稿に述べたような各種指標値を用いた客観的な重症度評価法の確立が是非とも必要である．

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特集：SIRS・sepsisの最前線

序：SIRS, sepsis, 敗血症の病態解明とsepsisに対する新規治療法の開発

相川直樹　　藤島清太郎

序：SIRS, sepsis, 敗血症の病態解明とsepsisに対する新規治療法の開発

相川直樹　藤島清太郎

Understanding the pathogenetic mechanisms of SIRS and sepsis and development of innovative therapies of sepsis

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Abstract

The concept of systemic inflammatory response syndrome (SIRS) was introduced in 1992 to define and objectively diagnose sepsis. Over the last decade, the definition of sepsis has been used for inclusion criteria of multicenter trials to develop innovative therapies of sepsis. With the recent understanding of the pathogenetic mechanisms of sepsis, many drugs have been tested, but only two drugs (activated protein C and neutrophil-elastase inhibitor) have been approved for clinical use in sepsis or SIRS. Further understanding of basic pathophysiology of SIRS and sepsis holds promise to develop a new therapeutic strategy to improve survival of patients with SIRS and sepsis.

Key words: SIRS, sepsis, cytokine storm, innovative therapy

はじめに

SIRS は systemic inflammatory response syndrome の略で，1991年に米国で開催された American College of Chest Physicians と Society of Critical Care Medicine の Consensus Conference（合意会議）で初めて提唱された臨床概念である．この会議を主導し，SIRS の考えを創造したのは後述する Roger Bone 教授であった．

sepsis の定義に関する合意内容が，1992年6月に両学会の機関誌である Chest[1] と Critical Care Medicine[2] に同時掲載され，SIRS の概念が広く注目されるようになり，今日まで，多くの研究によりその病態が解明されてきている．両機関誌の論文の表題が“Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis”となっているように，そもそも SIRS は sepsis の定義統一のために導入された概念である[3]．

SIRS の概念導入により sepsis が共通の定義（sepsis＝感染症を原因とする SIRS）で認識され，その簡便な診断基準により，ベッドサイドで sepsis が迅速に診断されるようになったことから，sepsis の新規治療法の多施設臨床治験が円滑に進むようになった．これを基に開発された SIRS や sepsis 新規治療薬が臨床応用されるようになるまでには長い年月を要したが，一つの臨床概念の導入が医療を変え得ることのモデルとなった．

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I. SIRSに基づいたsepsisの定義

1. sepsisの定義

このように，SIRSはsepsisとその関連病態の定義を統一する必要性から生まれた概念である．1980年代後半の北米において，sepsisやこれに伴うショック(septic shock)，多臓器不全(septic MOF)に対する新しい治療法として大量コルチコステロイドや抗エンドトキシン抗体などの新薬開発が盛んに行われるようになった．しかし当時はsepsisの定義が統一されていなかったために混乱が生じていた．

医師によってsepsisの定義や解釈が異なることは，臨床現場での混乱を招くばかりでなく，sepsisの多施設臨床治験におけるsepsis患者の選択基準設定に大きな支障であった．このような背景から，sepsisをめぐる用語の統一が求められていた[4]．

sepsisを'重症の全身症状を有する感染症'とすることにはほとんど異論はなかったが，sepsisの条件として，血液培養による病原菌検出を求めるべきか[5]，重症の全身症状とは，具体的に何の症状とし，どの程度の重症度とするかについては様々な意見があった．このような状況にあって，Boneはsepsisの定義を統一すべきであると主張して[6]，合意会議の議長として指導的役割を発揮した．

Boneは当初，自分が主張していた"sepsis syndrome"なる用語"を提唱しようとしたが，認められず，結局は，'感染症が原因となってSIRSとなっている状態'をsepsisとすることとなった．

2. SIRSの概念の導入と治験への影響

ここで，sepsisとsepsisでない感染症とを区別する'重症の全身症状'をどのように規定するかについては，全身性炎症を反映する4項目；体温(発熱または低体温)，心拍数(頻脈)，呼吸数(頻呼吸)あるいは$PaCO_2$($PaCO_2$低下)，末梢血白血球数(白血球増多または白血球減少)あるいは白血球分画(未熟顆粒球増加)のうち2項目以上に異常のある状態とし，これをSIRSとした．

SIRSの診断基準に必要な4項目の兆候や検査項目は，半世紀以上にわたって臨床現場で一般に用いられているものである．1992年の医療水準を考えると，sepsisを診断する根拠となる全身性炎症の診断には，例えばCRP，プロカルチトニン，インターロイキン6などの検査値をも取り入れれば，診断の精度が更によくなるとも考えられる．しかし，合意会議で提唱した診断基準は，上記の検査結果を待たなくとも，ベッドサイドで簡便かつ迅速に診断できるという点で，特にsepsisの新規治療薬の臨床治験の患者選択には有用となった．治験への組み入れ患者数が多くなるばかりでなく，sepsisの治療を早期に開始できることにより，治験薬の効果がより強く発揮されることが期待された．

一方，頻脈や頻呼吸は，炎症以外でも出現する兆候であり，これらで診断されるsepsis患者は，多様な病態からなる患者集団となることも指摘される[8,9]．このような多様な感染患者集団を対象とした治験では，治験薬の効果のみならず様々な要因が経過に影響し，そのノイズのために治験薬の有効性や安全性が正しく評価されないというジレンマもある．

3. Sepsisと敗血症の区別

合意会議によるsepsisの定義に従えば，感染症でSIRSとなればsepsisとなり，血中に病原微生物が存在しなくても'sepsis'とされる．例えば，急性気管支炎で38℃以上の発熱と白血球数12,000/mm^3以上とがあれば，血液培養が陽性でなくてもsepsisとされる．sepsisは邦語では敗血症と訳されるが，我が国ではこのような気管支炎を敗血症とはしない．

一方，邦語の'敗血症'は，一般に'重症の全身症状を伴う菌血症(あるいは真菌血症)'と定義されている[10]．特に内科領域や感染症領域で'敗血症'とするには，血液培養陽性が必要となる．抗菌薬が'敗血症'の適応を取得する場合にも，血中分離菌の推移が検討された症例が求められている[11]．

したがって，合意会議でのSIRSから定義される'sepsis'の登場により，'sepsis'と我が国で用いられている'敗血症'との間に乖離が生じ

てしまった．そのため，sepsisを敗血症と訳してしまうと，大きな混乱が生じる．そこで，著者は1992年以降の欧米の定義による'sepsis'は'セプシス'として，'敗血症'と区別するべきであると主張している[11,12]．

II. 病態の理解に基づく新規治療法

1. SIRSとsepsisの病態

sepsisを定義するために導入されたSIRSではあるが，SIRSの診断基準を満たす全身性炎症は外傷，熱傷，急性膵炎，ショックなどの非感染性侵襲でも惹起される．すなわち，エンドトキシンや外毒素などの病原微生物由来の物質のほかに，組織損傷やトロンビン形成，アノキシアなど種々の要因が全身性炎症の原因となり，原因が何であっても，同一の非特異的な全身性炎症が引き起こされる機序として，炎症性サイトカインをはじめとした種々のメジエータが関与することが知られてきた．

本特集では，その病態に関する最新の知見がまとめられており，その詳細は割愛するが，SIRSでは侵襲に対して，まずpivotal cytokinesとしてTNF-α (tumor necrosis factor-alpha: 腫瘍壊死因子)とIL-1(interleukin-1)の産生が増加し，主としてautocrine，paracrineであるべきサイトカインが，あたかもendocrineのごとく全身的に作用して，他のサイトカインやメジエータの産生を誘導し，全身性炎症反応のカスケードが広まることが病態の根源にある．敗血症のように高度の侵襲が持続する難治性重症感染症や，手術，外傷に続く感染のような繰り返す侵襲(two-hit)では，炎症性サイトカインの誘導・産生の制御機構が破綻し，種々のサイトカインが血中に高濃度出現，重症sepsisや多臓器不全(MODS)となる．sepsisでは種々のサイトカインが血中に高濃度出現することが知られており[13,14]，このような状態を，著者は'サイトカイン・ストーム'と称している[15,16]．

本特集では，SIRSとsepsisの複雑な病態生理学的機序についてproteomicsからgenomicsに至るまで多面的に解説されており，この数年にかけて膨大な情報が集約されてきたことがわかる．

2. 病態機序の理解に基づく新規治療法

多くの病態が解明されてきたとはいっても，SIRSとsepsisの病態は複雑多様であり，我々の知らない部分もいまだに多い．しかしながら，病態の理解に基づいた新規治療法が，最近になってようやく臨床応用されるようになった．この分野を研究している者として，大変勇気付けられる．

臨床医が病態生理を研究する目的にはいろいろあろうが，病態生理の研究成果が新規治療法の開発につながり，それにより患者が救命できることを目標にしている者も多い．抗菌薬療法が進歩した21世紀の今日でも，sepsisはまれな病態ではなくその死亡率は高く[17]，抗菌薬療法や感染対策に加えて，種々の新規治療法が開発されてきた．

合意会議で定義された重症sepsisの診断基準は，これらの開発において患者選択基準として使われてきたが，多くの臨床治験が失敗してきた中で[18]，新たにリコンビナント活性プロテインCが重症sepsisの死亡率を著明に減少させることが証明され[19]，欧米で認可され現在臨床現場で広く使われている．我が国でも，SIRSとALI(acute lung injury)の診断基準を用いて臨床治験が進められたエラスターゼ阻害薬が市場に登場した．

sepsisを定義するために創られたSIRSなる概念が，薬剤の適応症となるまでに12年を要したが，SIRSとsepsisの病態の理解は，今後も急速に進むことと思う．その成果が，新たな治療法導入につながり，sepsisの治療成績が目覚ましく向上する日も近いことと思う．

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特集：SIRS・sepsisの最前線

図説：高サイトカイン血症の病態生理

藤島清太郎　　相川直樹

図説

高サイトカイン血症の病態生理

Pathophysiology of hypercytokinemia

藤島 清太郎[1]　　相川 直樹[2]

SIRS(systemic inflammatory response syndrome)は，各種感染症や重症外傷，熱傷により惹起される全身性炎症反応である(図 1)[1]．SIRS 状態にある患者体内では，様々な炎症性，抗炎症性サイトカインが過剰に産生，放出され，これらが病態の形成に重要な役割を担っている(図 2)[2]．近年，サイトカインの概念は拡大傾向にあり，DNA 結合蛋白の一種である HMGB-1，可溶性受容体などもそれぞれ炎症性，抗炎症性サイトカインと認識されつつある．サイトカインは，各々特異的な受容体に結合し，paracrine，autocrine に標的細胞を活性化し，刺激伝達系酵素のリン酸化などを介して，様々な機能を発揮する(図 3)．ここでは好中球を例として，受容体(図 4)と，刺激時に放出されるメディエータ(図 5)を示した[3]．好中球は，サイトカインなどのメディエータによって活性化されると，接着分子を介して臓器内の微小血管内皮細胞に付着した後，血管外へ遊走し，組織内で上記傷害物質を放出して，急性肺傷害などの臓器不全を誘発する(図 6)．その中でも好中球エラスターゼは代表的な傷害物質であるが，近年同酵素に各種の細胞機能調節作用があることが明らかとなっている(図 7)[4]．

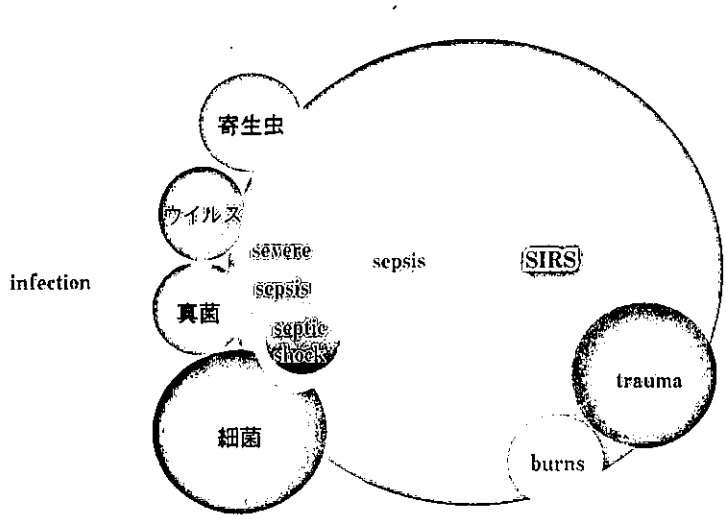

図 1　SIRS の概念と sepsis

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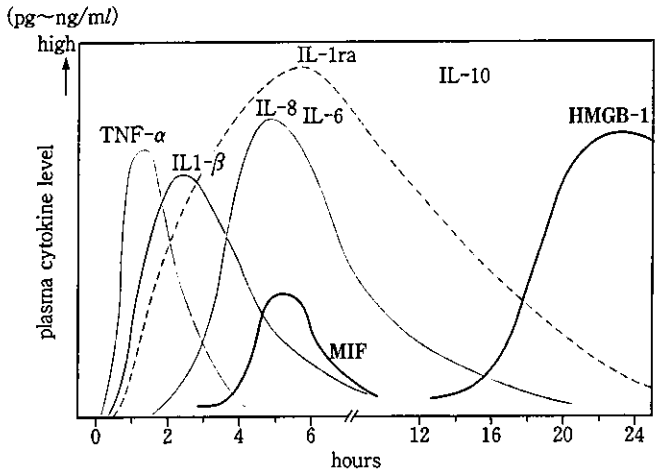

図2 Cytokine time course

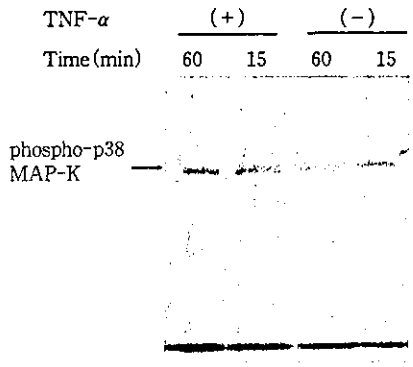

図3 TNF-α刺激後の phospho-p38 MAP-K 発現

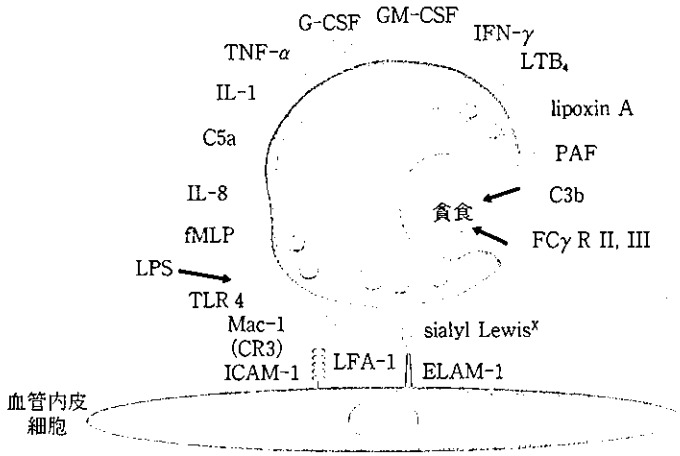

図4 好中球上の各種受容体と接着分子(文献[9]より改変引用)

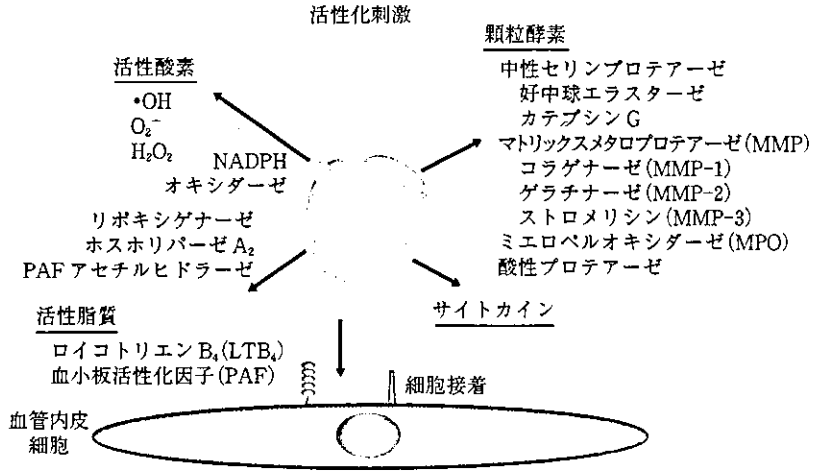

図5　活性化好中球の産生/放出物質と接着能(文献[3]より改変引用)

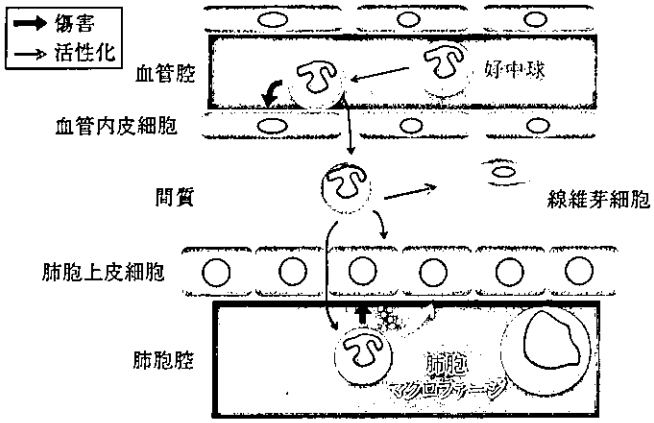

図6　好中球による急性肺傷害の発症機序

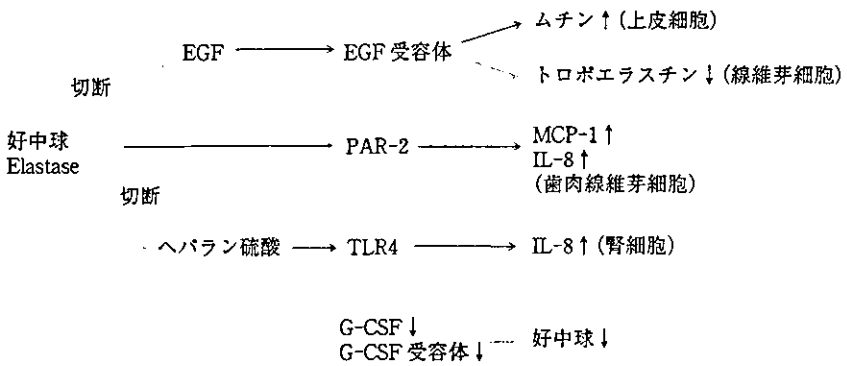

図7　好中球エラスターゼの各種遠隔作用

熱傷，大手術などの一次刺激後に感染症などの二次刺激が加わると，一次刺激のみの場合に比し強い生体反応が惹起される(two hit phenomenon)．著者らは，その機序の一部に，炎症性サイトカインの過剰かつ遷延性の産生が関与していることを見いだした[5]．図8において，熱傷前負荷マウスでは，無処置マウスに比べて血液，肺組織中のTNF-α，MIP-2(ヒトIL-8相当)が二峰性に産生亢進している．これらのマウスで認められた急性肺傷害は，サイトカイン産生抑制剤であるJTE-607，methyl-PSL投与により，有意に抑制された(図9)．

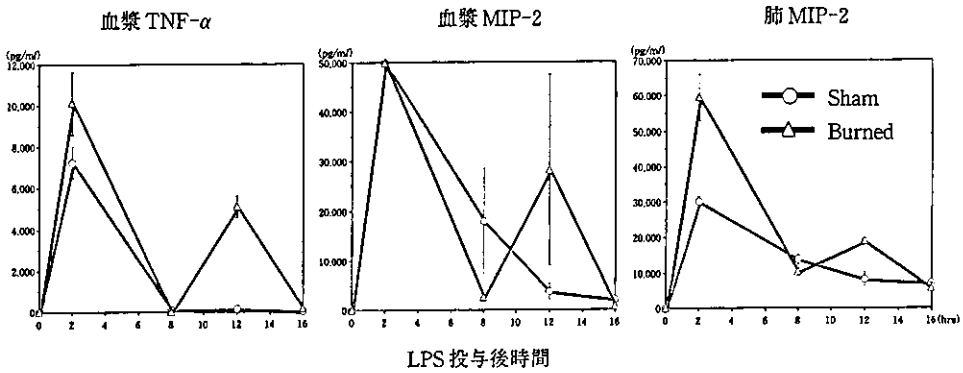

図8 対照および熱傷前負荷マウス血液，肺組織中TNF-α，MIP-2(文献[5]より改変引用)

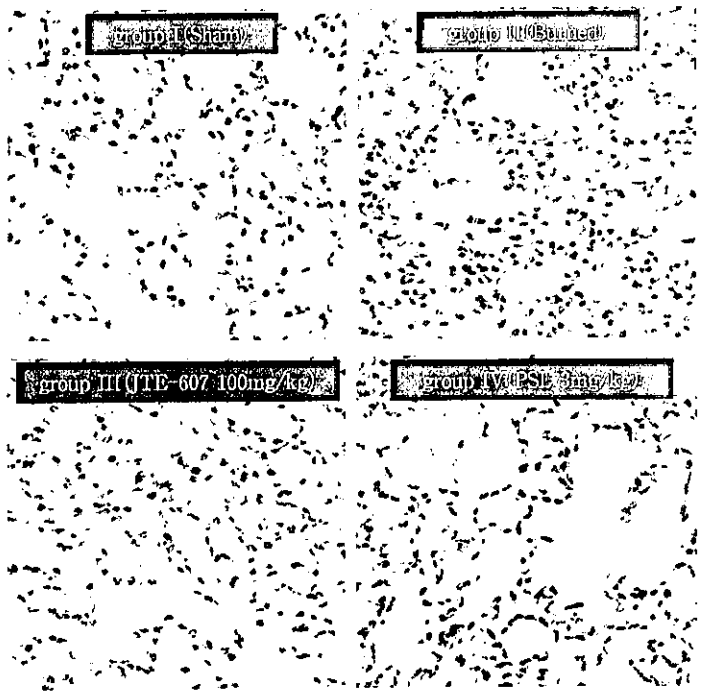

図9 肺組織所見(文献[5]より改変引用)

SIRS 患者血中で検出されるサイトカイン値は，患者間で大きなばらつきがある(図 10)．その一因として，サイトカイン遺伝子上に存在する遺伝子多型，特に一塩基変異多型(single nucleotide polymorphism: SNP)の関与が明らかとなっている．図 11，図 12 に TNF-α,β遺伝子多型，図 13 にシークエンスにより確認された IL-8 遺伝子上の SNP を示した．将来的には，これらの遺伝子多型を解析し，患者個々の特性に応じたオーダーメード治療を施すことが期待されている．

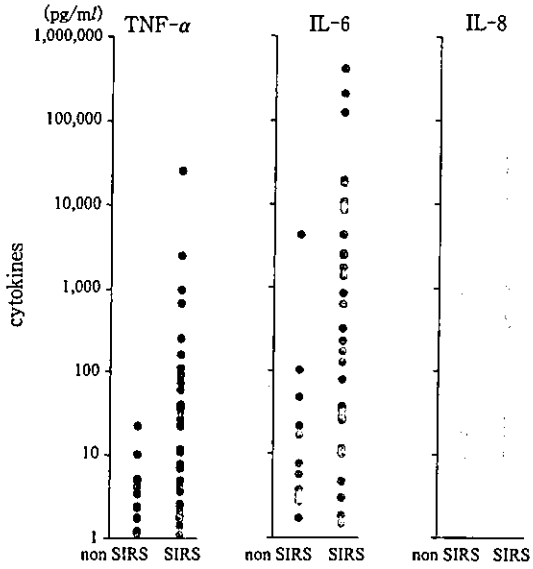

図 10 SIRS 病態下の血液中各種 cytokine 分布

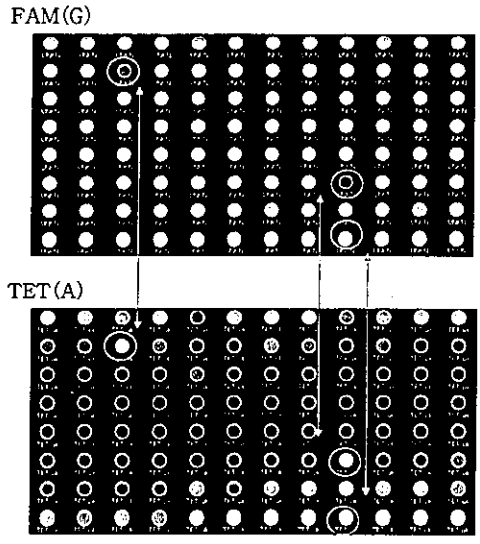

図 11 ABI Prism 7700 による TNF-α-308 SNP 解析

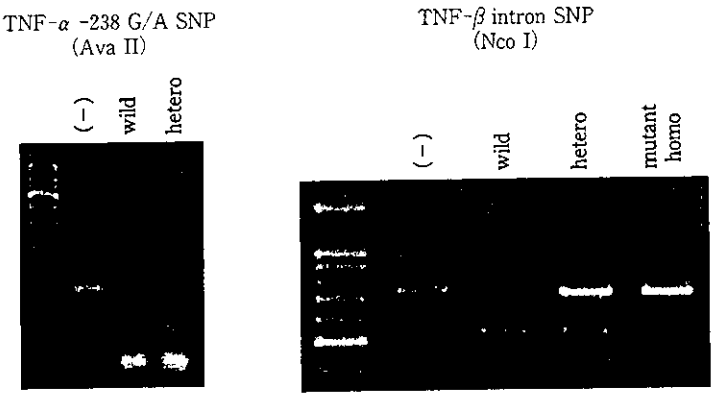

図12 PCR-RFLP法によるTNF SNP解析

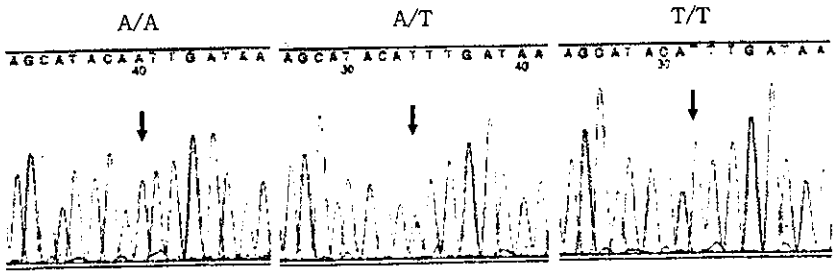

図13 Direct sequense法によるIL-8 promoter領域遺伝子多型の解析

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International Emergency Medicine

EMERGENCY MEDICAL SERVICES IN JAPAN: AN OPPORTUNITY FOR THE RATIONAL DEVELOPMENT OF PRE-HOSPITAL CARE AND RESEARCH

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□ **Abstract—Japan is at a crossroads in the development of its Emergency Medical Services (EMS). At present, Japan has an essentially pure scoop-and-run, defibrillation system. However, there is a strong movement toward expanding the scope of paramedic practice to include more complex, Advanced Life Support (ALS) and trauma protocols to its nationally standardized pre-hospital protocols. The implications of introducing complex pre-hospital protocols guided by the use of existing scientific evidence to support such action is discussed in the context of Japan's unique opportunity to test many fundamental questions in pre-hospital medical care and the public's understanding and acceptance of these practices. Japan, a technologically advanced country that is not encumbered by entrenched "standards of care," has the opportunity to develop an efficient and rational EMS system.** © 2005 Elsevier Inc.

□ **Keywords—EMS; pre-hospital; Japan; paramedic**

INTRODUCTION

Japan, a technologically advanced country of 130 million citizens, has a national Emergency Medical Services (EMS) system comprised of highly trained Emergency Life Support Technicians (ELST) whose complete protocols appear on six faces of a small, folded card containing the essence of their scoop-and-run-defibrillate pre-hospital philosophy. ELSTs in Hokkaido, Kyushu, or giant Tokyo—regions and cities differing in geography, transport distance, and epidemiology—are bound by the same protocols. A Japanese ELST can defibrillate ventricular tachycardia, perform CPR, and insert an oral-esophageal airway in a patient with no detectable vital signs. An ELST does not administer any drug, except for oxygen. On more than several occasions, we have heard and read that Japanese ELSTs and the Japanese public feel the pre-hospital scope of practice is severely limited compared with their counterparts in North America and other countries in the western hemisphere (1).

This is not altogether surprising. By contrast to the Japanese ELST, a comparably certified paramedic in New York City, population 8 million, has at least 58 separate protocols (2). Fresno County, California, which has a mixed rural, suburban and urban environment, has a population of just 750,000 people. Paramedics serving this diverse area have over 36 protocols, which run the gamut of advanced cardiac life support to the treatment of burns, snakebite, and seizures (3). Paramedics in Fresno, New York City, San Francisco or Houston, Texas can administer any one of 30 or more medications (from aspirin, adenosine, amiodarone and morphine all the way to terbutaline and verapamil) based on protocols developed and elaborated by EMS programs starting in the late 1960s and early 1970s. A paramedic in Maine or Sacramento, California can perform naso-tracheal intubation, a cricothyrotomy or decompress a tension pneumothorax using a thoracostomy needle. All U.S. para-

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medics can instill intravenous fluids in the setting of hypotension and trauma, yet, the evidence for the benefits of pre-hospital management of trauma using intravenous fluids remains controversial (4). Similarly, no clinical trial has yet proven that epinephrine or amiodarone improves survival to discharge from the hospital and the most rigorous clinical trials to date only suggest that endotracheal intubation might have a beneficial effect on overall survival in the setting of cardiac arrest, despite well-known and common complications associated with the procedure (5,6). In some regions of the United States, many pre-hospital practices are being scrutinized, with some being withdrawn or curtailed as data on the inefficacy or danger of certain pre-hospital practices have emerged (7–10).

In this article, comparisons of health care economics, health care culture, epidemiology, and topics such as continuous quality improvement (CQI) are generally avoided, though useful tools for comparison do exist (11). Although our focus is the scientific basis for developing EMS in Japan, it is important to recognize that politics, the emotional and economic cost to society, corporate financial profits, and decisions about what pre-hospital system is right for Japan all enter the equation. We emphasize that in Japan, EMS is an entirely publicly funded service and patients do not individually pay the expense of their ambulance ride to the hospital. Thus, the economic significance of expanded practice, training costs, and utilization are not small.

The development of EMS in Japan has some temporal and philosophical parallels to that in North America. The Meiji Empress founded the Japanese Red Cross during the Reformation and Japanese physicians developed field treatments for the sick and wounded during their wars and natural disasters of the 19th and 20th centuries (12). The first ambulance services were started in pre-World War II days by the Tokyo Police Department and were intended for trauma, rather than medically ill victims. In 1935, there were six ambulances in the old Tokyo City. In 1961, the first designated hospitals providing 24-h emergency services were assigned (13,14). The impetus for increased emergency services was twofold. First, an increase in the economic power of Japan was represented by an increase in car ownership—and in fatal car accidents, as well as a successful bid to host the 1964 Olympics. Thus, the first great expansion of ambulance services and designated emergency facilities was organized with the 1964 Tokyo Olympics in sight (15). Through the 1960s and into the early 1970s, emergency medical care in Japan was dominated by surgeons (14). It was not until 1973 that the Japan Association of Acute Medicine (JAAM) was founded, largely by surgeons, ironically with little collaborative effort between surgeons, intensivists, internists and members of other specialties wishing to provide comprehensive emergency services in dedicated emergency departments (EDs). In 1991, members of JAAM, other dedicated physicians, citizens and politicians collaborated to implement the Emergency Life Saving Technicians (ELST) Act (13). That same year saw the introduction of the privately and publicly funded Foundation for Ambulance Development. Japanese EMS, in contrast to the U.S. EMS system, is a government-sponsored service managed through the auspices of the Fire Department. In 2001, there were approximately 5517 ambulances (16). In contrast to U.S. EMS systems, even those run by fire departments, patients calling 119, the national equivalent to the U.S. 911, are not charged for the service of transportation to the ED.

In 2002, approximately 207 ambulance units of the Tokyo Fire Department, alone, made 629,883 runs in response to "119" calls. Of these, more than 50% were made for patients over the age of 50 years (17). Thus, as the Japanese population ages, the nation faces an important issue: What is the agenda for the future of EMS in Japan?

Two recent events have pushed the EMS development agenda to the forefront of the Japanese public's consciousness. The first event was in Akita City, where the practice of endotracheal intubation was being performed illegally by pre-hospital ELST units for several years. When this was revealed, and the paramedics indicted, the citizens of Akita City regarded the paramedics as heroes, stirring debate about their professional fates and the "backwardness" of Japanese EMS. A second occurrence, in November 2002, was the tragic, sudden cardiac death of Prince Takamadonomiya at the Canadian embassy in Tokyo. As a result, there has been public outcry to expand the scope of practice in Japanese EMS from its basic life-support-based system.

In response to these events, and recent research in Osaka Prefecture and Tokyo, the Ministry of Public Management and Home Affairs, along with Japan Medical Association and JAAM, formed three committees to address fundamental issues of EMS practice in Japan (18,19). The three committees are for: 1) defibrillation by paramedics, 2) endotracheal intubation, and 3) the use of drugs. Each committee is composed of 9 to 10 individuals representing different specialties and sectors of society. For example, the defibrillation committee was composed of two physicians from Emergency Medicine, one pediatrician and one from the Japanese Medical Society. In addition, there was one legal advisor, two members from the fire department and two from related bureaucracies.

COMMENTARY

Until the death of the beloved cousin of the Emperor, ELSTs could not defibrillate without consent of a base

hospital physician. This event, and the abundant data supporting the use of rapid defibrillation to save lives in the setting of cardiac arrest, accelerated the policy of defibrillation without calling into the base hospital (20–22). Since April of 2003, Japanese ELSTs have been interpreting, with the aid of interpretive computers, cardiac monitor rhythm strips in the setting of pulseless ventricular tachycardias and fibrillation. However, Japanese paramedics are still highly restricted in their scope of practice. They are trained in the basics of advanced life support (ALS) and basic trauma life support (BTLS). Thus, they may maintain and protect the airway using the bag-valve-mask (BVM), laryngeal mask airway (LMA), or esophageal obdurator airway (EOA, similar to combitube), but only in the setting of cardiac arrest. Because they are now permitted to defibrillate without consulting a base-hospital physician, ELSTs may avoid life-threatening delays in the use of semi-automatic defibrillators. Consistent with other interventions in the Japanese EMS system, ELSTs may only start intravenous lines and administer lactated Ringer's solution in the setting of cardiopulmonary arrest. These restrictions in practice are in sharp contrast to the wide variety of interventions used in North America.

Our observation is that in Japan, there is building popular and political pressure to rapidly expand the scope of practice of ELSTs to be more comparable to that of North American paramedics and other western EMS systems. Although appealing, this is bound to be an expensive and controversial undertaking. By expensive, it is meant threefold: in economic, social and professional terms. By controversial, we mean that many of the general practices of pre-hospital ACLS and BTLS, although appealing and empirically useful, have not necessarily been proven effective by prospective studies and, at this time, the most rigorous data are lacking (5,6,23–31). Thus, in the United States and in North America in general, there are 30 to 50 protocols for any paramedic to choose from in any given situation—many of which probably do not require attention in the span of an ambulance's arrival and delivery of the patient to an ED, especially in an urban setting with short transport times. The most fundamental questions in pre-hospital care seem to have the same foci: how much to do at the scene of an accident, a cardiac arrest, an acute exacerbation of a chronic illness? For most prehospital interventions, there is little evidence of a positive effect on outcome (23,31). However, shorter prehospital time—inherent in scoop-and-run systems such as that in Japan, has been shown to be a critical factor for patients with cardiac arrest and trauma activation of prehospital systems (32,33).

Japanese ELSTs, as well as many medical doctors, are professionals who truly believe that expanding their scope of practice will result in lives saved. All medical professionals, doctors and emergency life-saving technicians alike, are sincerely dedicated to the proposition that our first duty is not to harm the patient. Many members of the medical profession in Japan have met proposed expansions of EMS services with skepticism and resistance. Because policies are set at a national level, all cities and prefectures are subject to the policies set by the Ministry of Health. Many involved in pre-hospital medical services in Japan may harbor resentment toward the medical profession, which can be perceived as holding back EMS development for reasons not entirely related to patient care. It is our opinion that in the long run, the best chance to help patients and not harm them is to test each proposed intervention in a randomized (and when possible, blinded), controlled trial (RCT). This type of testing is the gold standard of clinical inquiry and minimizes bias. For conditions such as cardiac arrest, meaningful endpoints such as "survival to discharge" would be used, rather than the dubious "return of spontaneous circulation (ROSC)" or "survival to admission" (5,23,24).

We know from Japan's centralized, Utstein-based EMS databases that 5517 ambulance units made 4,399,195 runs in response to "119" calls in 2001. The mean response time from call to arrival on scene for 4,399,195 ambulance runs was 6.2 min (35). In the year there were 88,058 out-of-hospital cardiac arrests (16). Japan's EMS databases and hospital record keeping, and essentially pure scoop-and-run/defibrillate system make it well situated to perform first-rate pre-hospital science.

Thus, Japan has an opportunity to test many fundamental hypotheses important to the practice of pre-hospital patient care. Though there are legal barriers (e.g., nationally uniform pre-hospital practice laws that prevent local and regional clinical trials), and perhaps cultural ones as well, there is no standard of care to interfere with the ethical performance of randomized controlled clinical trials of interventions such as endotracheal intubation vs. "simple" hyperventilation by BVM, LMA or combitube. Similarly, there is no technical barrier to a trial of epinephrine vs. placebo. Even landmark studies such as the OPALS series from Canada have had to use retrospective controls (whose results are subject to the Hawthorne Effect type biases) (6,21,22,32). In Japan, methodological shortcuts can and should be assiduously avoided when possible and validated tools, such as the Utstein template and true randomization, should be standard and, fortunately, are already the basis for record keeping by Japanese ESLTs and their base hospitals (36).

The public, anywhere in the world, expects and deserves the protection that effective government oversight provides. Many arguments have been put forth suggesting that endotracheal intubation, vasopressors and antidysrhythmics, applied in certain pre-hospital settings,

may save lives (36,37). These interventions deserve the most rigorous scrutiny and testing (25).

Other interventions, such as pre-hospital administration of anti-seizure medications, oral dextrose for hypoglycemia, and morphine for the pain of a fractured long-bone indeed may be convenient and warrant less scrutiny, while broadening the repertoire of Japanese ELSTs in the field. The tenets of evidence-based medicine suggest that evidence from research is only one component to be considered in clinical decision-making, with individual clinical circumstances, patient and citizenry preferences, and clinician's expertise determining therapeutic action or restraint. When rigorous scientific evidence is lacking, yet years of clinical experience and acumen suggest an intervention is effective and safe, it is reasonable to try that intervention until there are data to suggest otherwise.

In the broader picture, basic questions are: whose judgment and under whose control will protocols be driven, based on what quality of evidence? How much money will be dedicated to research and how much time is needed for that research? Who will be accountable when patients come to harm through ELST error and how will policy disagreements be handled at a national level? (10,38) New interventions such as endotracheal intubation and the administration of potentially dangerous medications increase the complexity of the ELST's or paramedic's curricula and will likely add significant expense to the publicly funded pre-hospital system. In the United States (even with rapid sequence intubation), misplaced endotracheal tubes and multiple intubation attempts in the field are a common and dangerous occurrence (39–42). The limited *clinical* experience of technicians, lack of evidence for positive effects on outcome, and the prolongation of scene times the more interventions are introduced should be primary considerations before the scope of EMS practice is broadened. Furthermore, skills requiring the most technical knowledge—and judgment—deteriorate fastest, thus increasing danger to patients before they have ever arrived in the hospital where larger teams can work together with the ELSTs to clarify the patients' needs (43). Everyone needs to consider, also, the cost of expanded protocols in terms of drugs, equipment acquisition and maintenance, as well as extra training and re-certification costs. In Japan, if ESLTs are to start giving medications, their legal status as healthcare providers certified to do so will need to be revisited.

The "Chain of Survival" concept that is generally embraced should be based on rigorous evidence that the chain, in fact, improves survival and minimizes harm (44). In North America, we have a system that is based at least as much on tradition as on evidence. Invasive field procedures and risky medications may be overused due to the so-called "technical imperative." The technical imperative has been expressed as, "if a procedure can be taught, it will be used with a frequency greater than its indication" (45). Any system introducing new practices should consider this pitfall with the greatest of attention not only to the risks and benefits of such practices but to the adversarial relationship that may be created among physicians, nurses and paramedics (45).

Fortunately, there has been a recent surge in high quality pre-hospital research that might clarify long-standing controversies in EMS practice (7,21,22,32,44). Some research, which has been performed with rigor, could still introduce new practices prematurely due to overenthusiastic endorsement or over-interpretation about its applicability (46–48). Thus, individual studies showing promise for a particular therapy should be repeated before being put into general practice and sub-group analyses showing significant effects should be viewed with caution, though the finding may be excellent for hypothesis generation (48).

Opportunities for international collaboration to further the development of EMS in Japan, for its benefit and that of the rest of the world, abound. The results of systematic and rigorous scientific inquiry will surely benefit all Japanese citizens and help enlighten the practice of EMS worldwide. With good public education and a rational approach to EMS development, there is good reason for optimism that victims of cardiac arrest and other critically ill patients can be given optimal treatment or therapeutic restraint to optimize survival in the out-of-hospital setting (6,8,49). However, before the people of Japan commit vast amounts of time, money and emotion to an expanded EMS system, we urge caution and scientific rigor.

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Metabolism of hemoglobin-vesicles (artificial oxygen carriers) and their influence on organ functions in a rat model

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Abstract

Phospholipid vesicles encapsulating Hb (Hb-vesicles: HbV) have been developed for use as artificial O_2 carriers (250 nm ϕ). As one of the safety evaluations, we analyzed the influence of HbV on the organ functions by laboratory tests of plasma on a total of 29 analytes. The HbV suspension ([Hb] = 10 g/dl) was intravenously infused into male Wistar rats (20 ml/kg; whole blood = 56 ml/kg). The blood was withdrawn at 8 h, and 1, 2, 3, and 7 days after infusion, and the plasma was ultracentrifuged to remove HbV in order to avoid its interference effect on the analytes. Enzyme concentrations, AST, ALT, ALP, and LAP showed significant, but minor changes, and did not show a sign of a deteriorative damage to the liver that was one of the main organs for the HbV entrapment and the succeeding metabolism. The amylase and lipase activities showed reversible changes, however, there was no morphological changes in pancreas. Plasma bilirubin and iron did not increase in spite of the fact that a large amount of Hb was metabolized in the macrophages. Cholesterols, phospholipids, and β-lipoprotein transiently increased showing the maximum at 1 or 2 days, and returned to the control level at 7 days. They should be derived from the membrane components of HbV that are liberated from macrophages entrapping HbV. Together with the previous report of the prompt metabolism of HbV in the reticuloendothelial system by histopathological examination, it can be concluded that HbV infusion transiently modified the values of the analytes without any irreversible damage to the corresponding organs at the bolus infusion rate of 20 ml/kg.
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1. Introduction

Liposomes or phospholipid vesicles have been extensively studied for the application of drug delivery system, and some are now approved for a clinical use as antifungal or anticancer therapies [1]. Another promising application is to use vesicles for encapsulating a concentrated human Hb. The resulting Hb-vesicle (HbV) can serve as an O_2 carrier with ability comparable to red blood cells (RBC) [2–4]. The advantages of the Hb-based O_2 carriers (HBOCs) are the absence of blood-type antigens and transmission of known and unknown blood-borne disease, the possibility to improve the rheological properties of blood flow according to the needs of patients, and stability for long-term storage. These characteristics will make it possible to use the HBOCs both in elective and emergency situations [5,6]. In this sense, the infusion of HBOCs becomes superior to the conventional blood transfusion that still has the potential of mismatching, infection such as HIV and hepatitis virus, and the problems of only 2–3 week preservation period. The acellular Hb modifications including polymerized Hb and polymer-conjugated Hb are now undergoing the final stages of clinical trials [7,8]. However, the cellular structure of HbV (particle diameter, ca. 250 nm) most closely mimics the characteristics of natural RBC such as the cell membrane function of physically preventing direct contact of Hb

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