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CONTENTS

Micro-Manipulation and Micro-Robots

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Abstract: The author and Dr. Masayuki Nakao have been collaborating with clinicians from collegiate hospitals to develop a series of small three-dimensional structures to meet their special needs. So far, we have:

(1) Produced microchips for immunologic tests with 10 micron wide reaction grooves. The microchips reduced the testing time down to a hundredth of that of conventional tests.
(2) Developed a mechanical system for handling DNA.
(3) Built a multipoint electrode to embed in the brain for measuring acoustic potential.
(4) Developed an artificial voice generator and demonstrated that it can give vocal ability to speech-handicapped patients cordectomized by laryngeal cancer.
(5) Developed a micro-pump to aspirate pus from the middle ear, and applied it in surgery for patients with otitis media.

All these advances have demonstrated the benefits of collaboration between engineering and medical professionals.

Key words: Micro-manipulation; Micro-robot; Micro-chip; Micro-pump;
Brain electrode; Artificial voice generator

Introduction

The author and Dr. Masayuki Nakao (Department of Engineering Synthesis at the University of Tokyo) have been pursuing studies in the fields of information communications, and important medical care/bioscience. The philosophy behind our studies is the concept that "micro-devices will make the largest contributions to the society in the future" (Fig. 1).

At the same time, we fortunately became acquainted with many scientists including physicians, dentists, and genetic researchers to form teams for pursuing our cooperative studies.

We strongly believed that good collaboration and team work between engineers and medical scientists could contribute greatly to society, and this belief led us to develop a number of "micro-devices". Most of these devices were three-dimensionally structured and formed
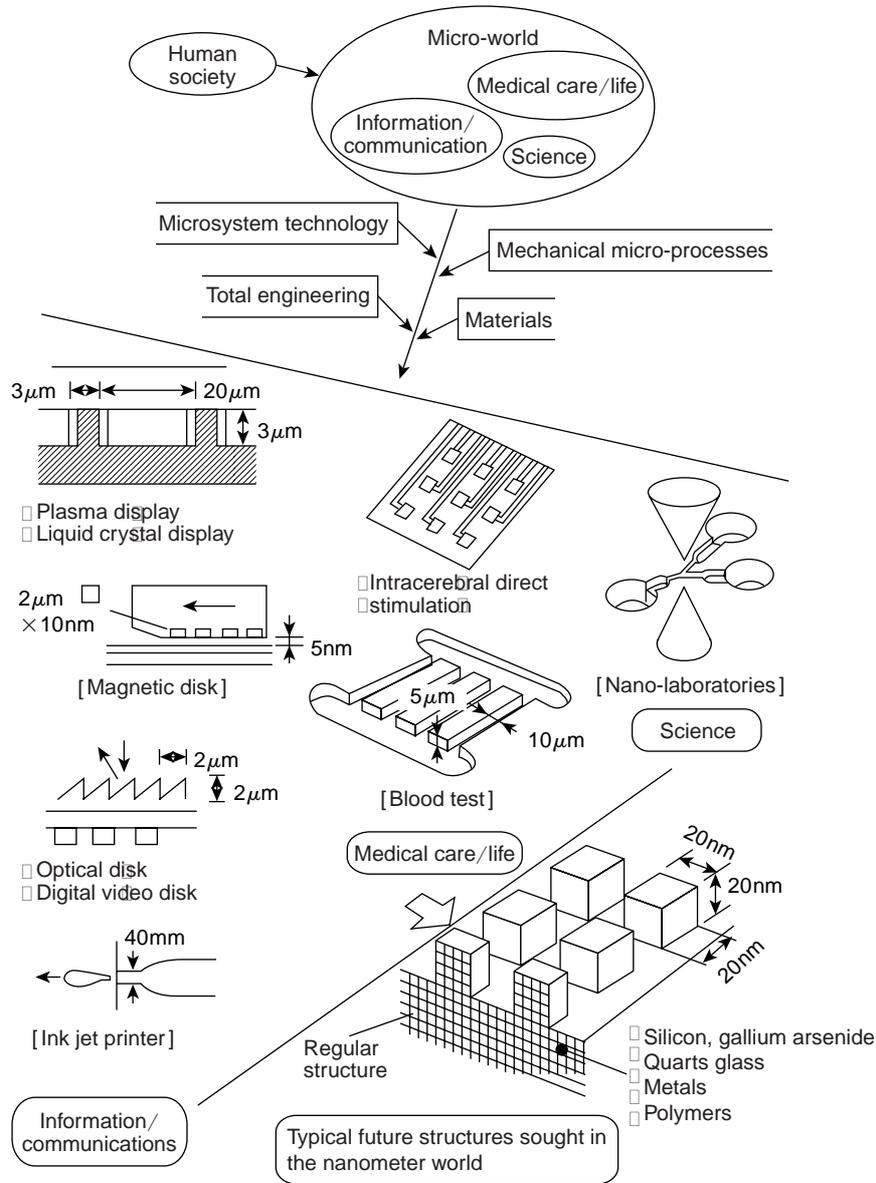
Fig. 1   The micro-structures-seeking worlds

with precision in the order of microns. We also developed methods for direct visual observation of these micro-devices during operations and handling, and achieved significant results.

Our major research contributions include (1) developing immuno-chips, (2) mechanically manipulating DNA, (3) embedding electrodes in the brain, (4) developing an artificial voice generation system, and (5) developing a micro-pump for surgery.

Although we have conducted research in many other areas, this paper provides an overview of these five research themes.

Research Themes

1. Immuno-chip

An Immuno-chip is a plate of glass with small grooves for positioning the subject material of immune reaction testing. Its small flow
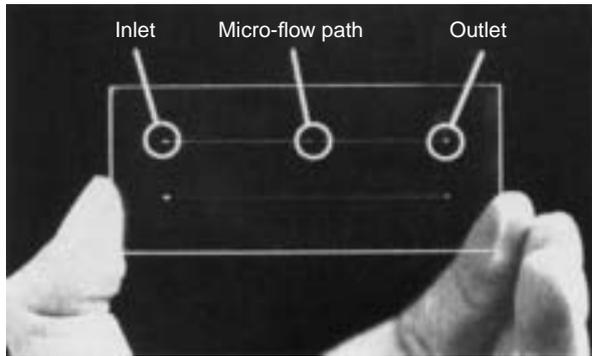
(a) External view of reaction plate
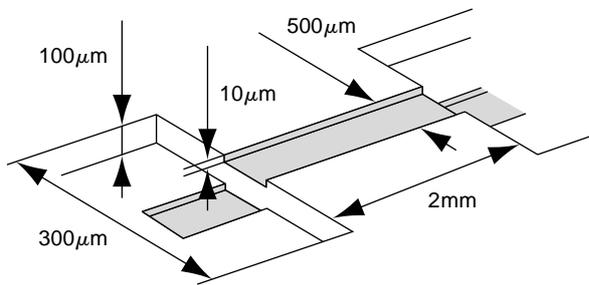
(b) Structure of a micro-flow path

Fig. 2   On-chip laboratory for immunologic assays

(a) Bulk   (b) On-chip lab.
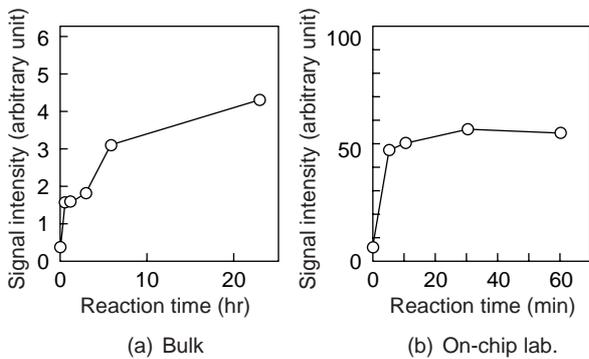
Fig. 3   Comparison of reaction time of test with anti-CEA rabbit antibody

Fig. 4   Schematic diagram of apparatus sending surface acoustic waves to chromosome
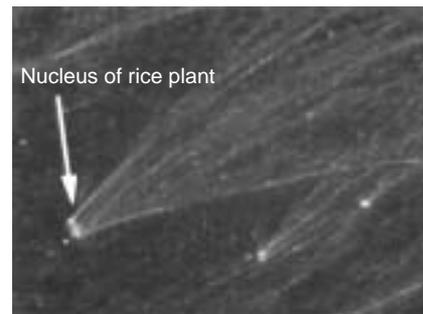
Fig. 5   Photomicrograph showing an extended chromosome

path, which is only several 10 micron grooves in size, allows fast reactions (Fig. 2). The test results are available within about 5 minutes compared to conventional testing that takes 24 hours. The chip takes advantage of the principle that reducing the size to 1/10 cuts down the reaction time to 1/100 (Fig. 3).

The conventional practice of waiting several days after the test before beginning surgery has changed to running the test during surgery; a big change in the medical practice.

2. DNA research

Our research into DNA is quite unique compared to other research conducted around the world. Typical studies identify their base sequences by cutting the DNA into small pieces and multiplying them. Our method disentangles the chromosome using enzymes (Fig. 4) to extract a single thread of DNA (Fig. 5). The procedure then fixes the entire DNA strand to
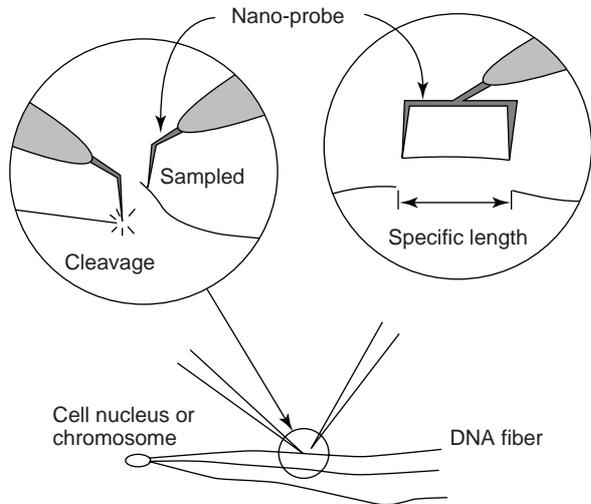
Fig. 6   Handling of DNA fibers

(a) Whole structure of the electrode
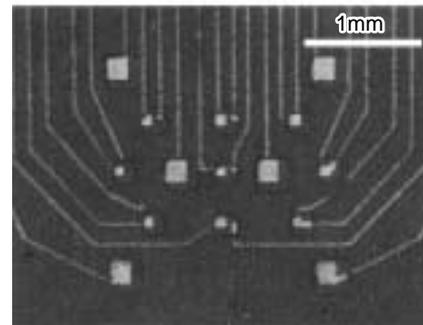
(b) Magnified view of the electrode tip

Fig. 8   Implantable electrode for brain stem

Fig. 7   Near field light microscope using a nano-probe

cut out the necessary part (Fig. 6) and reads the base sequence of the part cut out. This cutting requires special tools developed for this purpose. We are also building a near-field light microscope for direct observation of the DNA structure (Fig. 7).

3. Embedding electrodes

Production of micro-objects allows us to observe processes within the human body. For example, when sound enters the ear, we recognize it by an electrical signal that travels to the cerebrum. The motivation for our study was a desire to enrich the life of the hearing impaired by applying engineering means to directly repair the problem point, which may be anywhere along the external ear, internal ear, or path of the electrical signal to the brain, or within the brain itself.

Technology has already realized the wide availability of the artificial internal ear, which converts vibrations of the air into electrical signals for the hearing impaired. The next step, however, of revealing how the current is conveyed to the cerebrum, has not yet been adequately explored. We have developed an array of electrodes to embed in the brain (Fig. 8).

The embedding type electrode array has a number of small electrodes of sizes 20μm to 50μm. Embedding the electrode inside the cerebrum, the brainstem, or attaching it to the

cerebrum surface allows us to observe when and where the current runs and how the nerve system reacts upon hearing sound.

We are combining our research efforts with those of Dr. Tetsuo Ishii and Dr. Mikiko Takayama of the otorhinolaryngology department of Tokyo Women's Medical University, and Dr. Kimitaka Kaga of the otorhinolaryngology department of the University of Tokyo, in an effort to realize this most desirable technology for medical doctors.

4. Artificial voice generation system

Devices currently in use, for people who have had their vocal cords removed due to laryngeal cancer or other reasons, add artificial vibrations from under the chin to generate vocal vibrations.

Our research has its basis in an entirely different principle. Our idea was that, if lack of vocal cords was causing loss of voice, we could place a vibrator inside a tooth so that the person with the implant could form the mouth into the proper shape for vocalization. This idea advanced into planting a vibrator in the mouth to amplify the vocal sound the person makes.

Our future plans involve storing the voice prior to cordectomy and producing the same voice by amplifying even the smallest enunciation after the surgery.

The study is making steady progress, however, we are troubled by the problem of the wire hanging out from the mouth.

5. Micro-pump

In treating otitis media with suppuration, myringotomy usually results in a large incision in the eardrum because viscous pus is difficult to extract from inside. This procedure causes thickening in the tympanic membrane where the cut was made and hardening of the entire membrane. This causes the patient to have hearing difficulty even after the cut is healed. There is a need to keep the extraction hole in the eardrum small while effectively pumping out the viscous pus inside.
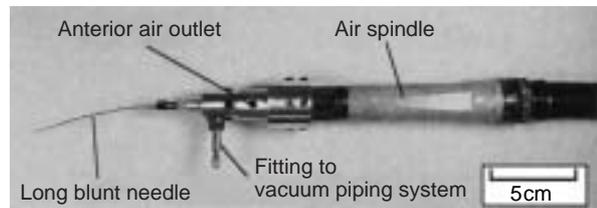
Fig. 9   External view of micro-caliber needle pump

Given these conditions, we developed a device that has a micro-spiral inside a 0.3 mm diameter injection needle which rotates at high speed to extract the viscous pus from inside.

The research continued for 7 to 8 years in pursuit of good results, and we are now working with researchers attached to a dental device manufacturer to commercialize the product for real use (Fig. 9).

Other Research Themes

Other research themes include, modifying an intravascular catheter to scratch out thrombus or embolus from blood vessels, and developing artificial insemination methods for inserting a sperm in the ovum with minimum disturbance. The latter involves microscopically holding down the ovum and inserting the sperm from a microscopically small opening. Another area of research involves measuring biting force using a sensor placed inside a molar.

Postscript

These researches require medical doctors and engineers to make joint efforts towards observing what many patients require, making suggestions, collaborating and merging the findings. Our research team at the engineering department of the University of Tokyo includes the author, who retired from the university in March of 2001, his successor Prof. Masayuki Nakao, and many other researchers who have been making cooperative efforts. These researches are, we feel, quite different from other

conventional studies.

I believe the most important aspect of these researches has been to make steps within the world of medical science towards contributing to and improving the lives of ordinary people.

We believe that micro-manipulation and micro-manufacturing to build and manipulate structures of 1 mm (1/1000 m), 1 μm, (1/1,000,000 m), and 1 nm (1/1,000,000 mm) are crucial, and this belief has pushed our researches.

"Micro" in general means small, but our word "micro-manipulation" signifies actual substances; the size of an atom is about 0.2 nm, and work in the nano-meter world is approaching the world of atoms.

We use the word "genome" when we think of DNA as a small unit of information. Objects composed of substances with the size of atoms determine the roots of people's lives. I believe that directly working on the smallest substance clarifies the mechanisms of life and eventually will lead to happiness for humankind. It is my greatest pleasure to work with the people in these fields and make contributions to medical science and human life.

Future Medicine in the Post-Genome Age
—Targeting tailored medicine for hypertension—

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Abstract: The release of the draft sequence of the whole human genome in 2001 is still fresh in our minds. In the post-genome era, a key concept "tailored medicine for common diseases" is proposed with a view to future medicine. The term "tailored medicine" means personal and optimized medical service for each individual, with low risks and high quality. Single nucleotide polymorphisms (SNPs), personal nucleotide alterations in the human genome, provide important information to clarify the pathogenesis of common diseases and advance the development of tailored medicine. We have examined various interactions between SNPs and hypertension or hypertensive complications to demonstrate genetic predisposition to salt sensitive hypertension in Japanese people. Furthermore, several preliminary results suggest that the effect of environmental factors was significantly different according to genotypes of SNPs. Achieving the stage of tailored medicine, physicians may in the future refer to the SNPs data of the patient as an aid to daily medical care.

Key words: Genetics; Polymorphism; Human genome;
Renin-angiotensin system; Salt sensitivity

Introduction

The draft sequence of the entire human genome released in the two leading science journals, *Nature* and *Science*, in February 2001 is still fresh in our minds. Genome is a general term denoting a basic set of DNA strands containing genes composed, by nature, of the four bases: guanine, adenine, thymine and cytosine. As is widely known, an entire human genome comprises approximately three billion base pairs, which, as elucidated by Drs. Watson and Crick, form the characteristic double-stranded helical structure. It was generally believed that approximately one hundred thousand genes are arranged on a human genome, but once the base

sequence was actually determined, it turned out that the number is limited to about thirty thousand genes. The published completion of a draft sequence has nevertheless revealed an arrangement of only a little more than 90% of constituent bases, whilst research on the roles of genes and their bearing upon disorders and disease states has just begun to take shape.

It is said that the oncoming era will be an age of analyses of the transcriptome, a general term for transcription products, or of the proteome, a general term for translation products. However, accurate understanding of the significance of the genome *per se* should be given priority when it comes to carrying out these approaches. We would also like to stress that the term "post-genome age" does not connote that genome analysis is completed; it only connotes that the human genome has been elucidated sufficiently enough to allow entry into a whole new paradigm of medicine.

Tailored Medicine

The term "tailored medicine" has been proposed as a keyword for the post-genome era. Tailor-made medical care means instituting the medical care that is best suited to the constitution of any given individual patient and is generally thought to represent medical care of the twenty-first century as distinct from the current form which is uniform for all patients.

Regarding hypertension, by way of an example, tremendous efforts have been devoted to the control of this disorder because of a high incidence of strokes, especially cerebral hemorrhage, in this country. These efforts led to success in achieving a substantial reduction in the incidence of cerebral hemorrhage through lifestyle correction and the development of various antihypertensive drugs. With the arrival of the super-aging society, however, the decline in incidence has already reached its ceiling and mortality from cardiovascular disorders has reportedly taken an upward turn. In the quest for a powerful solution for reducing deaths

from cardiovascular disorders, current research is being directed toward the elucidation of the pathogenesis of hypertension by gene analysis, the use of tailor-made medical care utilizing this information, development of new drugs based on genomic information, and exploration of the applicability of gene therapy.

Gene Analysis and Genetic Diagnosis

The form of hypertension that causes most cardiovascular diseases is essential hypertension, hence of unknown etiology. Three strategic techniques are currently used in analyzing of the genes responsible for essential hypertension, i.e., the linkage analysis, which analyzes familial aggregation of the disease using a pedigree; the sibling pair analysis, which analyzes identity by descent using affected or discordant sib-pairs; and the case-control study, which compares the genetic backgrounds of hypertensive subjects with those of normotensive subjects (Fig. 1). Linkage analysis using pedigrees is markedly useful in the study of rare monogenic hypertension such as Liddle's Syndrome and glucocorticoid-remediable aldosteronism, and has succeeded in identifying the gene mutations that cause disorders such as epithelial amiloride-sensitive sodium channel gene.[1]

A clear causal relationship exists between a gene and the development of a monogenic disorder inasmuch as hypertension definitely develops in the presence of a gene mutation. Gene analysis may thus be said to constitute genetic diagnosis in monogenic disorders. In the case of essential hypertension, which is a disorder of multifactorial causation, on the other hand, there is no clear causal relationship between an altered base sequence of the gene and hypertension. In hypertension, gene analysis merely demonstrates that the presence of a certain type of gene indicates a higher probability for developing the disorder. This type of gene, which bears an increased relative risk, is called a disease-susceptible gene, and the
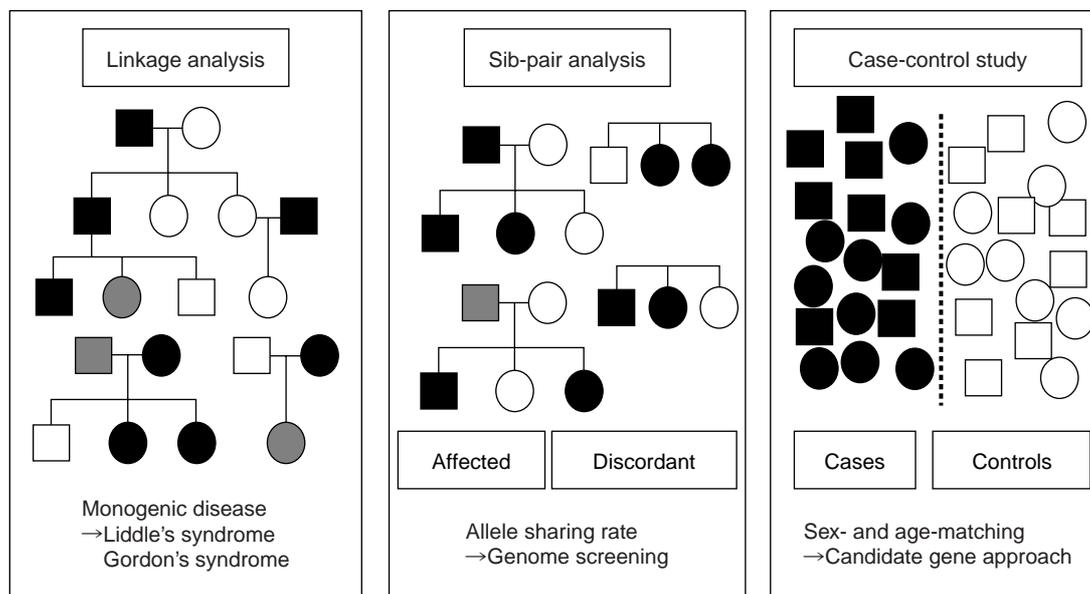
Fig. 1   Three strategic techniques of gene analysis

inter-individual differences in base sequence observed in the genome are referred to as genetic polymorphism. The ABO blood types are a good example of nucleotide polymorphism. Although peptic ulcer is more common among persons of blood type O, not all individuals with blood type O are predisposed to peptic ulceration; likewise, it should be understood that the results of analyses of genetic polymorphisms indicate a risk for hypertension but do not necessarily diagnose hypertension.

Gene Analysis of Hypertension and Gene-Environment Interactions

Large-scale genome screenings using sib-pair analyses have been conducted in Europe and the United States. In essential hypertension, any relevant single gene polymorphism appears to exercise a comparatively minor influence. However, it has been proven that it is difficult to isolate susceptible genes for hypertension even if thousands of sib-pairs are collected. Case-control studies comparing a hypertensive subject group with a normotensive subject group

are again in the limelight. We focused our attention on nucleotide polymorphism of the renin-angiotensin system using this approach. Our study has revealed that *TT* type gene polymorphism involving amino acid substitution of threonine for methionine, called *M235T* polymorphism at exon 2 of the gene coding angiotensinogen, has bearing on the family history of hypertension and on the non-dipper type hypertension characterized by a minor nocturnal decrease in blood pressure.[2]

With regard to the renin-angiotensin system, a thrifty gene hypothesis has been proposed. This hypothesis supposes that the renin-angiotensin system was originally essential for retention of sodium and water within the bodies of human ancestral species evolved from lower aquatic life,[3] and goes on to suggest that the advent of our satiated consumer age may have led to the increases in hypertensives and patients with cardiovascular complications. In support of the hypothesis, one may note that the *TT* type accounts for 100% of chimpanzees, for 90% of an African hominid thought to be a close ancestor of human beings, and for more

—Japanese vs. Caucasians—

Angiotensinogen
T235

Japanese	81
Caucasians	45

(Ishikawa, *Hypertension* 2001)

α-Adducin
Trp460

Japanese	57
Caucasians	15

(Ishikawa, *Am J Hypertens* 1998)

Aldosterone synthase
T-344

Japanese	69
Caucasians	50

(Tsujita, *Hypertens Res* 2001)

G protein β3 (Na-H pump ↑)
T825

Japanese	52
Caucasians	25

(Ishikawa, *Am J Hypertens* 2000)

(unit: %)
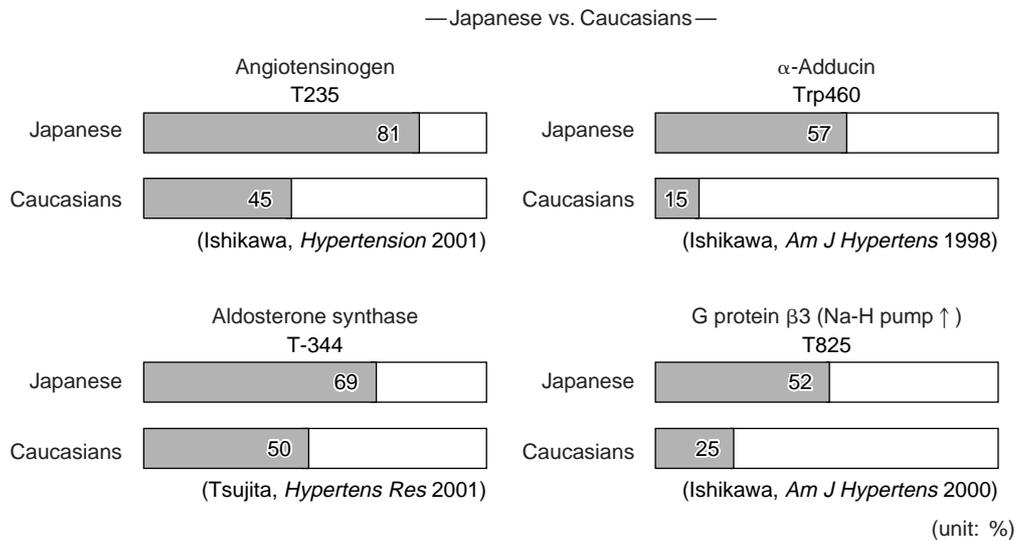
Fig. 2　Allele frequency of genes related to salt sensitivity

than 70% of Japanese. This may explain why salt-sensitive hypertensives are more common among Asian and Negroid people. In fact, a large prospective epidemiological survey on Caucasians with normal high blood pressure revealed that *TT* type subjects on an ordinary diet had a higher probability of developing hypertension whereas *TT* type subjects who actively followed a low sodium diet program had increased blood pressure less frequently than subjects with *MT* or *MM* genotype.[4] It would thus be advisable, using the application of the angiotensinogen gene *M235T* polymorphism to tailored medicine, for *TT* type subjects to be positively guided toward low-sodium intake while an earlier institution of antihypertensive drug therapy should be considered for subjects with *MT* or *MM* genotype.

The relationship between angiotensinogen gene polymorphism and salt sensitivity is a good example indicating the importance of gene-environment interactions. As for the interrelation of salt sensitivity and genes, it has recently been revealed that genetic polymorphisms of α-adducin, aldosterone synthase, G protein β3 subunit, etc. are also related to salt sensitivity.[5] Interestingly, all allele frequencies of salt sensi-

tive genes are higher in the Japanese population than in Caucasians, suggesting that the Japanese may be a hypertensive race with an intrinsically high sensitivity to salt (Fig. 2).[6,7] A strict low sodium diet would be the first step to tailor-made medicine for Japanese people.

Furthermore, based on the results of genetic polymorphisms of endothelin 1 and β2 adrenoceptors, it has also been revealed that blood pressure elevation associated with obesity varies with genotype.[8] It thus follows that obese individuals liable to high blood pressure may have to be positively guided to weight reduction. Other findings from gene analyses include the fact that angiotensin-converting enzyme gene polymorphism constitutes a potential hypertensive risk for males alone[9] and that some young females with angiotensin II type 2 receptor gene polymorphism are genetically invulnerable to hypertension. From these findings, it should be understood that essential hypertension is characteristically an intricate disease state etiologically composed of environmental and genetic factors and that correctly ascertaining the particular environment within which a given genomic information is meaningful will lead to tailored medicine.

Pharmacogenetics

Pharmacogenetic approaches are another way of utilizing gene polymorphism. It has become increasingly clear that the effects and incidence of adverse reactions to drugs vary widely with genetic polymorphisms ranging from enzymes directly involved in drug metabolism in individuals to the above-mentioned renin-angiotensin system. The utilization of this information is expected to be most powerful in the selection of effective antihypertensive drugs as well as in warding off serious adverse reactions. We have demonstrated that the efficacy of angiotensin-converting enzyme inhibitors administered for prevention of post-PTCA coronary artery restenosis varies with the genotype of insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) gene (Fig. 3).[10] Gene therapy that corresponds to the polymorphism in the promoter region may prove effective where gene polymorphism is involved in transcriptional control. Gene therapy for alteriosclerosis obliterans, a complication of hypertension or diabetes, has been initiated at our department, and we also intend to make use of genetic data in gene therapy for ischemia in the heart or brain.

Millennium Project

In gene analysis, the collection of accurate clinical information and of adequate specimens constitutes a key factor in the clarification of the relationship between a subject's clinical information and gene polymorphism. For hypertension for which genetic relative risk is low, cases and controls that represent both ends of a general population, e.g., severe hypertensives and apparent normotensives, are required to enhance statistical power. Ideally, a group of subjects that form a population should be gathered within the same geographical region.

To pursue this type of large-scale case control study and genoepidemiologic research, a national cooperative study system, which has
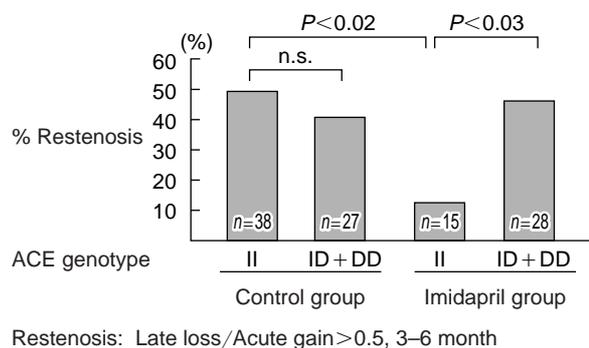
Fig. 3 ACE gene polymorphisms and the effect of ACE inhibitor on post-elective PTCA coronary restenosis[8]

been designated as a millennium project, has been organized and preparations for the elucidation of genes sensitive to hypertension and other lifestyle-related disorders are underway. More than a hundred thousand single nucleotide polymorphisms (SNPs) have already been identified out of the entire human genome, and genomic screening utilizing these SNPs are about to start. Several dozen hypertension-sensitive genes are expected to be verified by the year 2005. Therefore, tailored medicine based on the information on gene polymorphisms sited above may perhaps be in practical use at clinics by the year 2010.

Ethical Problems and Perspectives

Ethical issues are an important factor in the process of conducting these gene analyses and cannot be avoided. The triministerial joint ethical guidelines for human genome analysis were issued in March 2001, under which the preparation of a research protocol and obtaining informed consent are mandatory. The confidentiality of personal information must be maintained, and further, providing an accurate explanation to study subjects, attaining their understanding of inheritance, genes and gene polymorphism, giving a full explanation and obtaining their consent regarding retention of specimens and handling of analytical results are all compulsory.

Another task lies in the technological innovation for determining a vast number of genetic polymorphisms. While conventional techniques involved comparatively large quantities of specimens and manipulations, for example, enzymatic processing and electrophoresis, less costly procedures for genotype identification such as the TaqMan PCR method and the Invader technique requiring minute quantities of specimens are under development. Once information on the minimum number of polymorphisms needed to analyze Japanese subjects is gained, together with the development of bioinformatic, the development of DNA chips that enable an instantaneous analysis of information on several hundred thousand gene polymorphisms will no longer be a dream. Moreover, once such an era is inaugurated, individuals may carry their personal gene polymorphism information with them like credit cards, to which the attending physician may refer to provide daily living guidance and individualized drug selection.

Objectifying tailored medicine not only effectuates optimal medical care but is also expected to lead to the prevention of malpractice and reduced medical expenses. Practically no one had predicted such widespread use of cell phones and video games throughout the country before the present-day developments in information technology were realized. In the most desirable medical care of the post-genome age, gene analysis and gene therapy will not sound peculiar to patients or to general practitioners and will probably be handled matter-of-factly.

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Stem Cell Transplantation as a Mode of Regenerative Medicine

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Abstract: Advances in stem cell biology have made it possible for organ regeneration to become a reality, and this new technique is poised to enter the field of clinical medicine. The stem cells used in regenerative medicine are classified as embryonic or adult. Neurons, vascular endothelial cells, skeletal muscle cells, cardiomyocytes, osteoblasts, and chondroblasts have already been obtained from stem cells in the laboratory setting. Embryonic stem cells are amenable to mass culture and have versatile pluripotency but tend to be associated with problems in clinical application, including tumorigenesis, immunological rejection, and ethical issues. Since adult stem cells are obtained from the bone marrow of the patient, problems related to donors, ethics, rejection, and tumorigenesis do not apply. However, techniques for the isolation and *in vitro* amplification of adult stem cells have yet to be established, raising issues that await future solutions. For stem cells to be used in the clinical setting, regeneration at the tissue level is necessary, requiring the combined resources of tissue engineering and material science. Regenerative medicine is expected to play a leading role in 21st century medicine. However, the integration of studies from various scientific fields seems necessary for success in this area.

Key words: Embryonic stem cells; Adult stem cells; Regenerative medicine; Cell transplantation; Cardiomyocytes

Introduction

This paper outlines the current status and future prospects of regenerative medicine, particularly with regard to the use of stem cells. This new field of medicine has attracted a great deal of attention and is at the cutting edge of 21st century medicine. It is well-known that when a limb or tail of a newt or lizard is cut off, the missing part is regenerated from the stump. This occurs because cells at the cut edge can dedifferentiate into immature, pluripotent stem
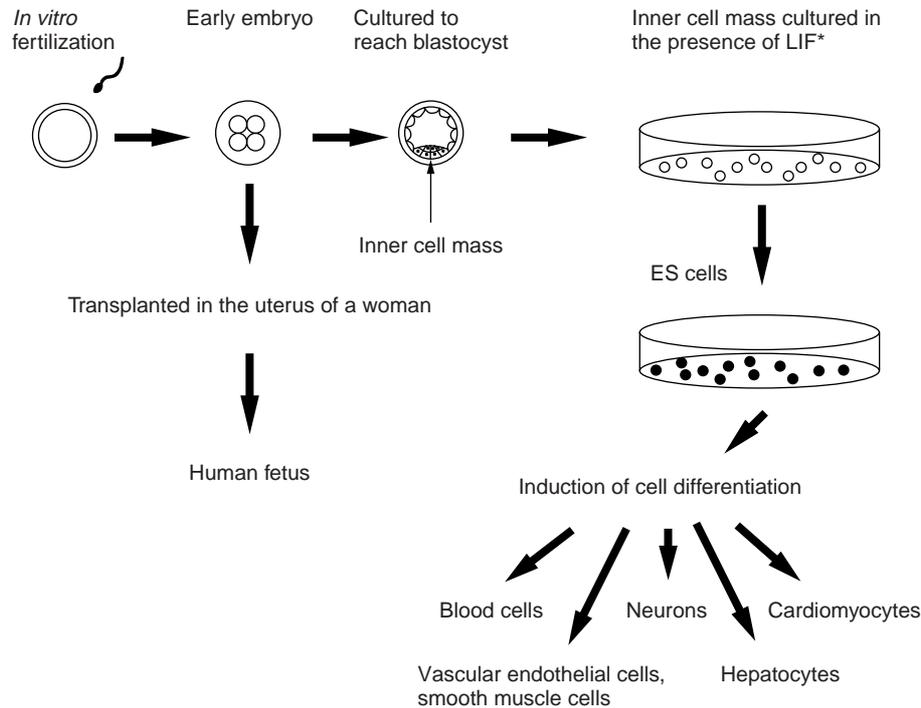
Fig. 1 Establishment of ES cells and their application to regenerative medicine

cells, and then differentiate again into the target cells after cell division and proliferation. Although this regenerative phenomenon does not occur in mammals, it does not necessarily mean that humans and other mammals lack regenerative capacity. Human somatic cells also include pluripotent stem cells, which are capable of proliferating and differentiating to repair tissue when an impairment or defect has occurred that leads to dysfunction of the organ. The aim of regenerative medicine is to treat disease and injury by making use of this capability.

Heart transplantation, which has been the main treatment option for severe heart failure, provides an example. Although heart transplantation is an excellent treatment, it is not widely employed because of the need for a donor and the possibility of rejection after transplantation. In contrast, regenerative medicine uses stem cells to induce the formation of cardiomyocytes, which are then transplanted to the impaired heart of the patient.

Stem cells used in regenerative medicine

Stem cells that can be used for regenerative medical therapies are broadly divided into two groups: embryonic stem cells (ES cells) obtained from early-stage embryos and adult stem cells that still are present in the adult body. These two types of stem cells have their own particular advantages and disadvantages. Whether one type is superior to the other remains controversial, depending on the type of tissue to which they are to be transplanted. A method of culture has already been established for ES cells, and their particular advantage is that they are capable of differentiating into any type of cell within the body.

Current status and problems of regenerative medicine using ES cells

At present, the regeneration of neurons,
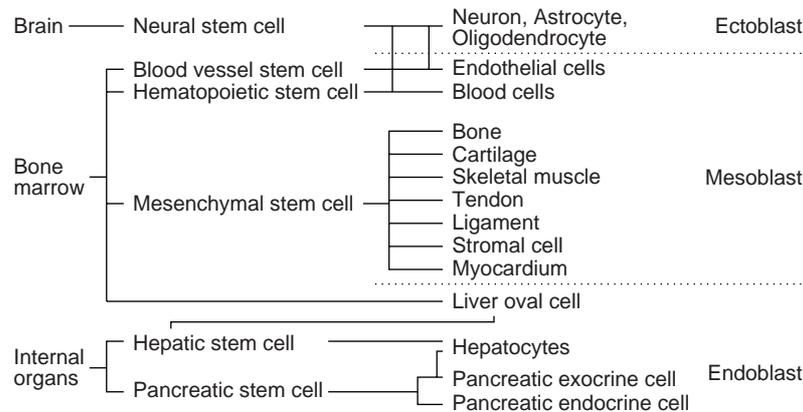
Fig. 2   Classification of stem cells in adults

blood cells, vascular endothelial cells, cardiomyocytes, pigment cells, osteoblasts, and islet cells is feasible or trying to be developed (Fig. 1). In theory, ES cells can differentiate into any type of cell in the body. However, in the actual setting, cells that occur in the early stage of development are fairly easy to obtain, whereas those that have undergone advanced differentiation in the late prenatal or postnatal period are more difficult to obtain. In addition, among neurons, large cells such as spinal cord ventral horn cells are considered easier to obtain from ES cells than from adult stem cells.

Although ES cells represent a very attractive tool from the viewpoint of tissue regeneration, they are associated with a number of drawbacks. First, because the ES cells used in allogeneic transplantation are obtained from others, rejection reactions cannot be avoided. Immunosuppressive therapy is required to manage the rejection, but such therapy may cause the quality of the patient's life to deteriorate and lead to high, ongoing medical expenditures. Second, if undifferentiated cells are present among the transplanted cells, it is possible that a malignant tumor, teratoma, may form in the tissue undergoing transplantation. In general, rejection reactions are more likely to occur in organs where blood flow is abundant, leading to a higher possibility of cellular infiltration.

On the other hand, from clinical experience with the transplantation of fetal midbrain obtained through artificial termination of pregnancy into the nigrostriatum in patients with Parkinson's disease, it has been found that about one month of immunosuppressive therapy is sufficient for cases of transplantation of allogeneic nerve cells into the brain, because lymphocytes cannot cross the blood-brain barrier. Thus, ES cells are presumed to be superior for the regeneration of nerve cells in the central nervous system.

Application of adult stem cells to regenerative medicine

Let us now turn to the other type of stem cells, adult stem cells. To begin with, stem cells are known to be characterized by their capacity for self-replication, proliferative potency, and pluripotency.

Stem cells are ranked from high to low in terms of the diversity of their ability to differentiate. For example, ES cells, which can differentiate into any type of cell, are given the highest rank, whereas hematopoietic stem cells are ranked in the middle, and cutaneous stem cells are considered low-ranking stem cells or precursor cells. Somatic tissues are formed from endoblasts, mesoblasts, or ectoblasts in the

fetal stage (Fig. 2). Skin and nerve tissues are derived from ectoblasts, and the stem cells of these tissues are therefore present in local areas. More specifically, cutaneous stem cells are present in the granular layer of the dermis, and neural stem cells are present around the cerebral ventricle of the cerebral hippocampus, where they are responsible for the regeneration of the respective tissues. Visceral organs such as the liver and pancreas are derived from endoblasts, and the stem cells of these tissues are present in the respective organs. If the liver is excised, oval cells or small hepatocytes in the remaining liver proliferate to regenerate the liver.

Various other cells of the body, such as bone, cartilage, fat, ligament, tendon, skeletal muscle, myocardium, and smooth muscle, are derived from mesoblasts. Among the stem cells of these tissues, some exist in muscle, for example, satellite cells, which are low-ranking stem cells found in the skeletal muscle. However, recent studies have revealed that the stem cells of these tissues are present in the bone marrow. As is well known, bone marrow consists mainly of hematopoietic stem cells and other cells of the blood cell series, but cells which are not blood cells are also present in bone marrow. Called bone marrow stromal cells, these cells are known to secrete various cell growth factors and cytokines that control the proliferation and differentiation of the blood cell series.

In recent years, it has become apparent that mesenchymal stem cells in the bone marrow with pluripotent capacity are present among marrow stromal cells. It had been reported by the early 1990s that mesenchymal stem cells differentiate into osteoblasts, chondroblasts, and adipocytes, and these cells began to be referred to as mesenchymal in the sense of mesoblast-derived stem cells. Since mesenchymal stem cells are stem cells for mesoblast-derived cells, we wondered whether they could differentiate to become cardiomyocytes, and we carried out studies along this line. We demonstrated that cardiomyocytes that beat

regularly by themselves could be obtained from mesenchymal stem cells. It has also been reported that mesenchymal stem cells can differentiate into mesoblast-derived tissues such as tendon and ligament.

At this point, it is important to determine to what extent these stem cells in bone marrow are pluripotent and how far they can differentiate. Results were reported in the U.S. last year of an autopsy case of leukemia in a female patient who died after the transplantation of bone marrow from a male donor. In this patient, cells possessing the Y chromosome derived from the male donor were found in liver, skeletal muscle, and the intestinal tract. Thus, it became apparent that adult stem cells can differentiate not only into mesoblast- but also into endoblast-derived organs. A more recent study demonstrated that mesenchymal stem cells can differentiate into ectoblast-derived nerve cells. Therefore, the expression "mesenchymal" is no longer accurate, and these cells have been called adult stem cells because they can differentiate to become tissues derived from any germ layer.

Current status of regenerative medicine using adult stem cells

What procedures, then, are necessary for enticing these stem cells to differentiate into the target cells? The procedures naturally vary according to the cells that are desired. For instance, differentiation into osteoblasts that produce bone can be induced by adding dexamethasone, ascorbic acid, and β-glycerophosphite to the culture medium. To obtain differentiation into chondroblasts, the presence of insulin, transferrin, proline, and sodium pyruvate is required. Thus, selective differentiation can be induced by using known growth factors, biological substances, or even chemical substances in some cases. For those cells for which an established procedure does not currently exist, the use of differentiation inducers is now an option.
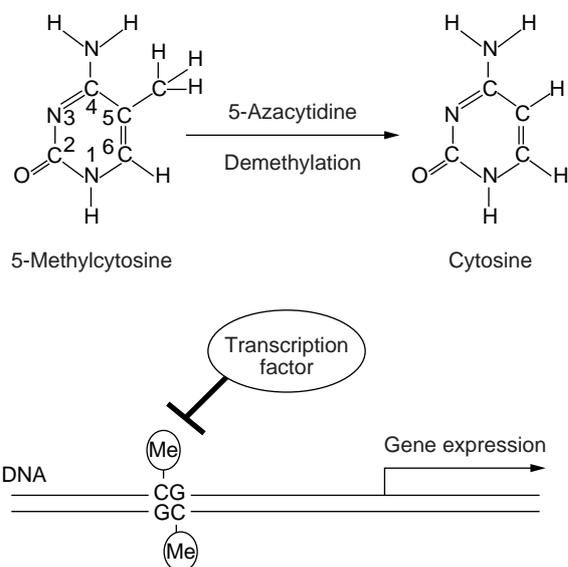
Fig. 3   Demethylation of DNA and differentiation of stem cells

When cytosine radicals on DNA are methylated, transcription factors cannot be bound to them, and, therefore, gene expression is inhibited. If the methylated cytosine radicals are demethylated by 5-azacytidine, various genes are activated, leading to differentiation of stem cells.

Me: Methyl radical

Although various differentiation-inducing agents are now available, we prefer a demethylating agent of DNA, 5-azacytidine. Details of its mechanisms of action, however, will not be discussed here. With this agent, it is possible to induce stem cells to differentiate into various directions through the random activation of transcription factors. From among the cells that have differentiated along various lines, those suitable for the particular purpose should be selected and utilized for the regenerative medicine procedure (Fig. 3).

Another method is to infuse stem cells directly into the target organ or tissue, to cause tissue regeneration. In each tissue, paracrine cytokines and growth factors are secreted from the surrounding cells, and tissue-specific cell adhesion factors and extracellular matrix are also expressed. Differentiation is induced by placing stem cells in such situations. Such a local environment is called a "niche". It is expected that the niche will induce the infused stem cells to differentiate in the same direction as the surrounding cells.

Adult stem cells are advantageous in that they are present within the bone marrow and their collection causes no organ loss to the donor. Further, the already well-developed bone marrow bank system theoretically makes possible HLA-compatible transplantation. Another advantage of adult stem cells is that the ethical issues surrounding them are far fewer than those related to ES cells. In addition, if the bone marrow of the same patient is used, there is no posttransplantation rejection or any need for immunosuppressive drug therapy, providing another great advantage.

Problems associated with adult stem cells

One problem associated with adult stem cells is that they are present in small numbers in the body, occurring at a rate of one in several hundred thousand marrow cells. The success of regenerative medicine using adult stem cells depends on whether they can be collected efficiently and proliferated under *in vitro* conditions while maintaining their pluripotent capacity.

Second, the problem of how to induce stem cells to differentiate into target cells is an important issue. Aside from particular cells for which the method of differentiation of stem cells is already known, further close investigation is necessary to establish methods of differentiation into various other cells present in the body. Another area of further investigation is to determine to what extent it is possible to induce differentiation in the niche by direct transplantation of stem cells in the target organ. Although the use of the niche is feasible for some organs such as myocardium and skeletal muscle, it is extremely difficult at present in the case of complexes of multiple types of cells, such as those comprising liver, lung, and kidney.

Use of tissue engineering and material science

Finally, it should be stressed that regenerative medicine has a very close relationship with tissue engineering and material science. Even if target cells can be obtained by using stem cells, they will need to possess a form consistent with their purpose when transplanted into the patient's body. For example, even if vascular smooth muscle cells are regenerated, blood vessels are not necessarily formed. For the cells to take the form of a blood vessel, a scaffold should be created from high-molecular-weight compounds that would dissolve slowly in the body. The cells should be placed on the scaffold and incubated to achieve the form of a blood vessel. The development of good materials for such scaffolding is another important aspect of the regenerative medicine.

Conclusion

Regenerative medicine has become an important focus of the medical profession in the 21st century. However, the success of this type of medical care will require the cooperation of various fields of science, including molecular biology, developmental biology, embryology, anatomy, tissue engineering, and material science. People have high expectations of regenerative medicine. It is therefore important that basic research and translational research that applies the results of basic research continue to make progress.

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Prehospital and Hospital Care of Acute Coronary Syndrome

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Abstract: The pathologic conditions caused by total or subtotal occlusion of the coronary artery as a result of the disruption of coronary plaque and subsequent thrombus formation are known as acute coronary syndrome (ACS). In determining treatment policies, it is important to differentiate between acute myocardial infarction and other conditions. For this purpose, biochemical tests that measure troponin and heart-type fatty acid-binding protein (H-FABP) as well as CK-MB are useful. In the treatment of ACS, hospital care that takes into account the severity of the disease should be based on an evaluation and stratification of risks. As antianginal drug therapy, the use of non-dihydropyridine Ca antagonists should be considered in addition to continuous intravenous infusion of nitroglycerine, antiplatelet drugs, and β-blockers, in view of the fact that the frequency of coronary artery spasm is high in Japanese patients. Although percutaneous coronary intervention (PCI) is thought to be useful for the treatment of drug-resistant ACS, no general consensus has been reached as to the timing of such intervention. A prospective intervention trial on this issue will be necessary in this country.

Key words: Acute coronary syndrome; H-FABP; Troponin T

Introduction

In 1992, Fuster *et al.*[1,2] defined the pathologic conditions caused by total or subtotal occlusion of the coronary artery as a result of the disruption of coronary plaque and subsequent thrombus formation as acute coronary syndrome (ACS). This syndrome includes unstable angina, acute myocardial infarction, and ischemic cardiac death. Since the benefit of thrombolytic therapy differs, these conditions are broadly divided on the basis of the electrocardiogram into the type with ST-segment elevation and the type with non-ST-segment elevation. In this paper, ACS of the type with electrocardiographic non-ST-segment elevation will be described, with reference to the relevant ACC/AHA guidelines.[3]
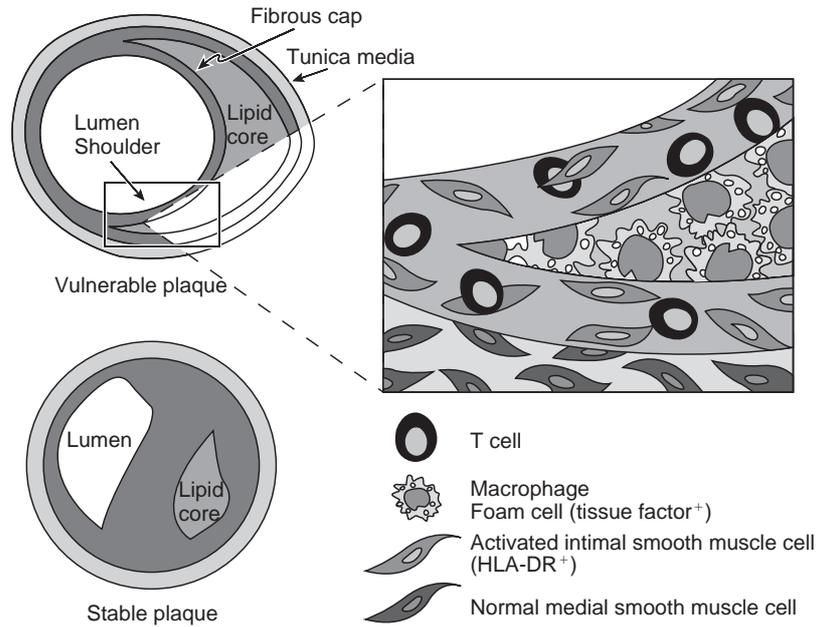
Fig. 1   Vulnerable plaque and stable plaque
(Libby, P.: Molecular bases of the acute coronary syndromes. *Circulation* 1995; 91: 2844–2850)
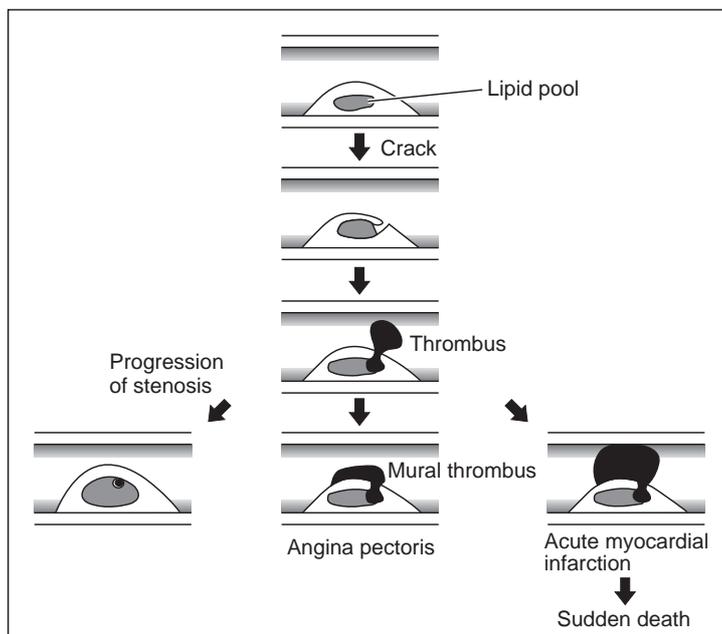
Fig. 2   Occurrence of acute coronary syndrome associated with plaque disruption
(Fuster, V. *et al.*: The pathogenesis of coronary artery disease and the acute coronary syndromes (2).
N Engl J Med 1992; 326: 310–318)

Table 1 Diseases That Should Be Differentiated from Acute Coronary Syndrome

Circulatory disease	Acute myocarditis, acute pericarditis, prolapse of mitral valve, acute aortic dissection
Lung disease	Pulmonary infarction, spontaneous pneumothorax, pleurisy
Gastrointestinal disease	Esophagitis, esophageal spasm, acute gastritis, gastric ulcer, cholelithiasis, cholecystitis, pancreatitis
Orthopedic disease	Pain derived from bone, cartilage, or muscle
Mental disease	Cardiac neurosis

ACS with Non-ST-Segment Elevation

1. Disease status

Rupture of vulnerable coronary atherosclerotic plaques plays an important role in the pathogenesis of ACS. A fibrous cap overlies the plaque and vascular lumen. The boundary area between the lumen and lipid core is considered liable to disruption in vulnerable plaques (Fig. 1). If a crack occurs in the cap to cause plaque disruption, thrombus formation is elicited, leading to ACS. Depending on the grade of thrombogenesis and plaque disruption, the patient may develop stable effort angina or unstable angina, or progress to acute myocardial infarction and sudden death (Fig. 2).

2. Diagnosis and differentiation

In history taking, it is important to obtain the features of chest pain, particularly "since when" and "under what situations" the patient recognized the pain, and "for how long" it continued. Immediate emergency treatment may be necessary depending on the frequency and duration of chest pain. Chest pain may not necessarily be typical, but may be attributable to diabetes mellitus. Some cases are pain free. Therefore, it is necessary to obtain the patient's past history and associated risk factors. Table 1 shows diseases with chest pain that require differentiation from ACS.

Electrocardiography (ECG) is indispensable for early diagnosis, and it is particularly important to observe changes in the electrocardiogram. When ACS is suspected, electrocardiography should be repeated at intervals to allow comparison. Diagnosis should not be based on the results of a single resting ECG.

Among blood biochemical tests, CK-MB (creatine kinase MB isoenzyme derived from the myocardium) is currently in wide use as a serum marker of myocardial injury. However, it has certain limitations in specificity. When ACS is suspected, serial rather than one-point measurement seems to increase the diagnostic value of the test. Heart-type fatty acid-binding protein (H-FABP) is considered useful for diagnosing hyperacute myocardial infarction. Cardiac troponin T and troponin I are more sensitive and specific than CK-MB. The effectiveness of a simple rapid diagnostic kit has been demonstrated, making it the diagnostic standard for acute myocardial infarction. This test is recommended in guidelines issued in western countries.

Table 2 shows biochemical myocardial markers for patients with suspected ACS in whom no ST-segment elevation is found on the 12-lead ECG. In addition to forming the initial diagnosis on the basis of clinical history, physical findings, 12-lead electrocardiogram, and biochemical myocardial markers, it is necessary to determine the severity of the condition (Table 3) to formulate treatment policy and to consider necessary measures (Fig. 3).

Prehospital Care

If a patient reports chest discomfort by telephone, no assessment should be made at that

Table 2 Biochemical Cardiac Markers of the Evaluation and Management of Patients with Suspected ACS but Without ST-Segment Elevation on 12-Lead ECG

Marker	Advantages	Disadvantages	Point of Care Test Available?	Comment	Clinical Recommendation
CK-MB	1. Rapid, cost-efficient, accurate assays 2. Ability to detect early reinfarction	1. Loss of specificity in setting of skeletal muscle disease or injury including surgery 2. Low sensitivity during very early MI (<6 h after symptom onset) or later after symptom onset (>36 h) and for minor myocardial damage (detectable by troponins)	Yes	Familiar to majority of clinicians	Prior standard and still acceptable diagnostic test in most clinical circumstances
CK-MB isoforms	Early detection of MI	1. Specificity profile similar to CK-MB 2. Current assays require special expertise	No	Experience to date predominantly in dedicated research centers	Useful for extremely early (3–6 h after symptom onset) detection of MI in centers with demonstrated familiarity with assay technique
Myoglobin	1. High sensitivity 2. Useful in early detection of MI 3. Detection of reperfusion 4. Most useful in ruling out MI	1. Very low specificity in setting of skeletal muscle injury or disease 2. Rapid return to normal range limits sensitivity for later presentations	Yes	More convenient early marker than CK-MB isoforms because of greater availability of assays for myoglobin Rapid-release kinetics make myoglobin useful for noninvasive monitoring of reperfusion in patients with established MI	Should not be used as only diagnostic marker because of lack of cardiac specificity
Cardiac troponins	1. Powerful tool for risk stratification 2. Greater sensitivity and specificity than CK-MB 3. Detection of recent MI up to 2 wk after onset 4. Useful for selection of therapy 5. Detection of reperfusion	1. Low sensitivity in very early phase of MI (<6 h after symptom onset) and requires repeat measurement at 8–12 h, if negative 2. Limited ability to detect late minor reinfarction	Yes	Data on diagnostic performance and potential therapeutic implications increasingly available from clinical trials	Useful as a single test to efficiently diagnose NSTEMI (including minor myocardial damage), with serial measurements; clinicians should familiarize themselves with diagnostic "cutoffs" used in their local hospital laboratory

CK-MB: creatine kinase MB isoenzyme derived chiefly from the myocardium

MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction

(From ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction, *JACC* 2000; 36, as were Table 3, Fig. 3 and Fig. 4.)

time. Rather, the patient should be told to come to the hospital. The initial diagnosis and treatment policy should be determined at the time of the patient's visit. Initial treatment is required even before the treatment policy has been established.

Table 3 Short-Term Risk of Death or Nonfatal MI in Patients with UA

Feature	High Risk (At least 1 of the following features must be present)	Intermediate Risk (No high-risk feature but must have 1 of the following features)	Low Risk (No high- or intermediate-risk feature but may have any of the following features)
History	Accelerating tempo of ischemic symptoms in preceding 48 hrs	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20 min or relieved with rest or sublingual NTG)	New-onset CCS Class III or IV angina in the past 2 wk with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema, most likely related to ischemia New or worsening MR murmur S3 or new/worsening rales Hypotension, bradycardia, tachycardia Age>75 y	Age>70 y	
ECG findings	Angina at rest with transient ST-segment changes. 0.05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions. 0.2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Markedly elevated (eg, TnT or TnI>0.1 ng/ml)	Slightly elevated (eg, TnT>0.01 but<0.1 ng/ml)	Normal

UA: unstable angina; MI: myocardial infarction; CABG: coronary artery bypass grafting;
CCS: Canadian Cardiovascular Society; ECG: electrocardiogram; TnT: troponin T; TnI: troponin I
An estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA is a complex multivariable problem that cannot be fully specified in a table such as this. Therefore, the table is meant to offer general guidance and illustration rather than rigid algorithms.
(Adapted with permission from Braunwald, E., Mark, D.B., Jones, R.H. *et al.* Unstable angina: diagnosis and management. Rockville, M.D.: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994; AHCPR Publication No. 94–0602. AHCPR Clinical Practice Guideline No. 10, Unstable Angina: Diagnosis and Management, May 1994.)

1. Primary care

(1) Antianginal drug therapy

As antianginal drug therapy, a sublingual tablet or spray of nitroglycerine and subsequent continuous intravenous infusion of the drug should be carried out while monitoring blood pressure reduction. Since a number of different guidelines indicate that the administration of nitrates is contraindicated for patients within 24 hours after taking sildenafil (Viagra®), it is necessary to determine that no sildenafil has been employed during that period. If chest pain persists, the use of β-blockers under pulse rate and blood pressure

monitoring should be considered. In addition, since the frequency of coronary vasospasm is high among Japanese patients, the use of a non-dihydropyridine calcium antagonist (diltiazem) is also effective, taking into account its prophylactic benefit.

(2) Antithrombotic drug therapy

Aspirin therapy should be initiated as soon as possible unless the patient is hypersensitive to the drug or has gastrointestinal bleeding. The therapy consists of an initial dose of 162–325 mg/day, followed by prolonged administration of 50–100 mg/day. Heparin is reported to be beneficial when combined with aspirin

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                        ┌─────────────────────────────┐
                        │  Symptoms suggestive of ACS  │
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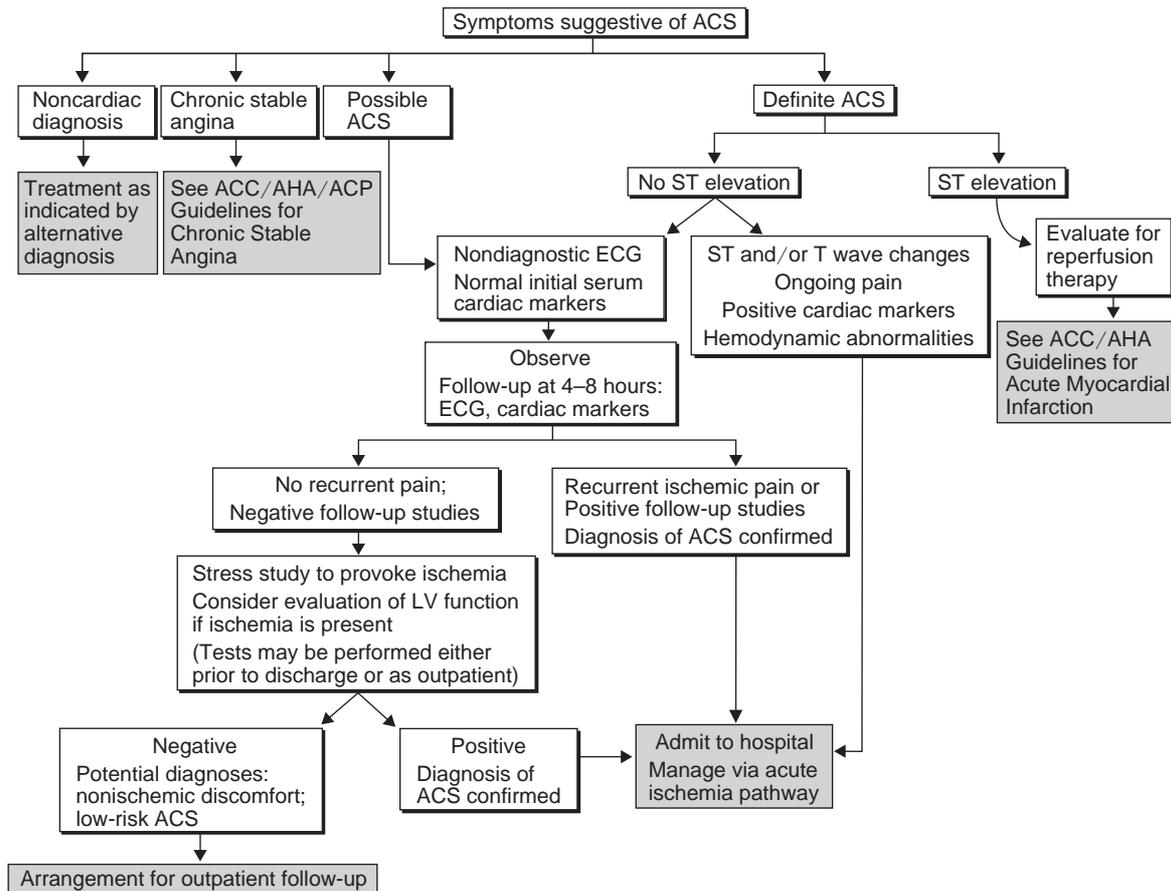
Fig. 3 Algorithm for evaluation and management of patients suspected of having ACS
ACS: Acute coronary syndrome; ECG: Electrocardiogram

in comparison with heparin monotherapy. Although not approved in Japan, GP IIb/IIIa inhibitors are also promising antiplatelet drugs. However, further testing and consideration of indications is necessary for this class of drugs because differences in their efficacy according to the method of administration have been noted.

2. Hospitalization and patient transfer

If symptoms do not improve, and even if the patient's condition is stable, hospital care needs to be based on the severity of the patient's disease. Timely transfer to a medical institution for admission, or to a CCU if possible, should be considered.

Hospital Care

1. Intervention

For patients with ACS who have recurrent ischemic events that are resistant to drug therapy, emergency coronary angiography/intervention aimed at revascularization should be considered. However, there are several different views as to the timing of elective coronary angiography/intervention in patients with stable ACS of the type with non-ST-segment elevation, and no general consensus has been reached (Fig. 4).

Coronary angiography/intervention as an early invasive strategy within 24 hours after onset has merit, in that the severity of the lesion can be confirmed before aggravation of

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┌─────────────────────────────┐
│ Recurrent ischemia and/or   │
│ ST segment shift, or        │
│ Deep T-wave inversion, or   │
│ Positive cardiac markers    │
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              │
              ▼
┌─────────────────────────────┐
│ Aspirin                     │
│ Beta blockers               │
│ Nitrates                    │
│ Antithrombin regimen        │
│ GP IIb/IIIa inhibitor       │
│ Monitoring (ryhthm and ischemia)│
└─────────────────────────────┘
       │              │
       ▼              ▼
┌──────────────┐  ┌──────────────────────┐
│ Early invasive│  │ Early conservative   │
│ strategy      │  │ strategy             │
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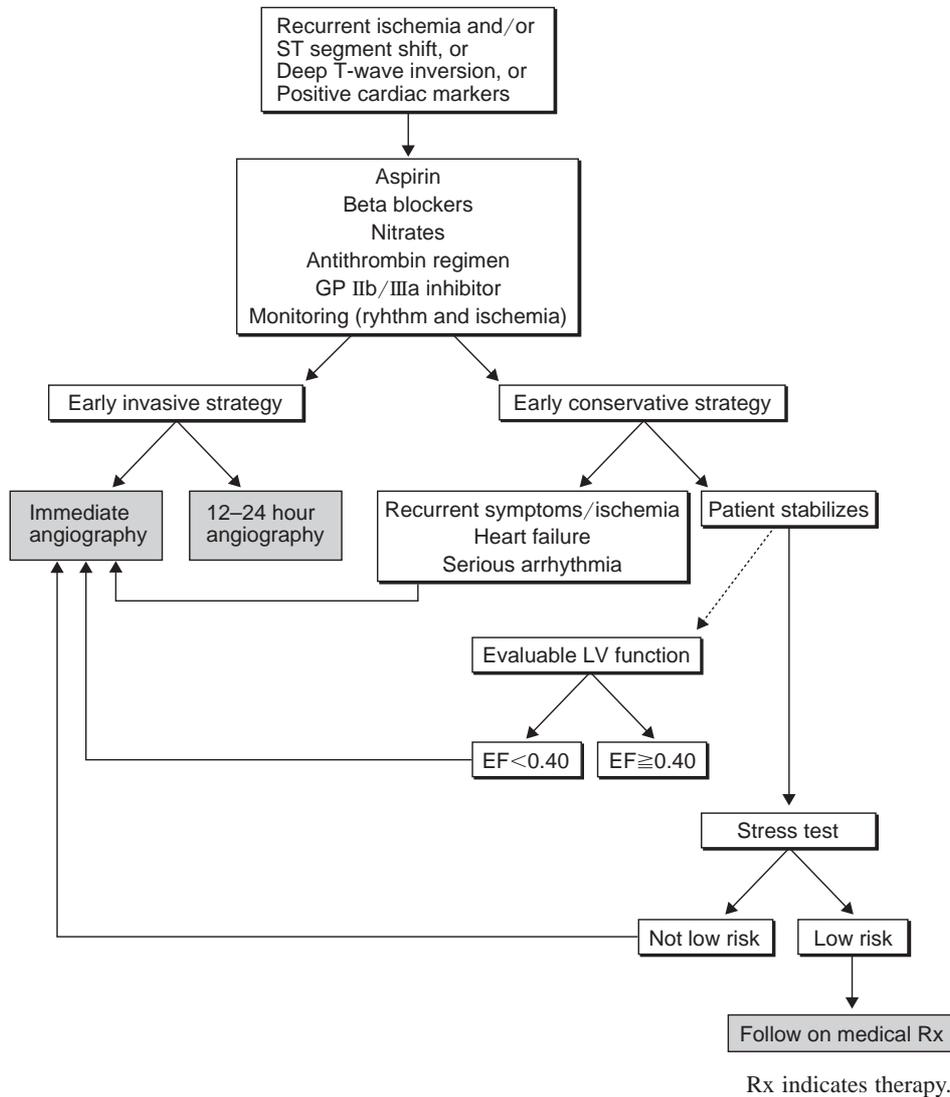
Fig. 4   Acute ischemia pathway

- Immediate angiography
- 12–24 hour angiography
- Recurrent symptoms/ischemia / Heart failure / Serious arrhythmia
- Patient stabilizes
- Evaluable LV function
- EF<0.40
- EF≧0.40
- Stress test
- Not low risk
- Low risk
- Follow on medical Rx

Rx indicates therapy.

the disease to allow risk stratification and decision-making as to treatment policy. On the other hand, the early conservative strategy has merit in that invasive tests and treatment can be avoided if ischemia is controlled by medical treatment after the patient is out of the acute phase, and if high risk is denied. In Japan, attention to the cost-effectiveness of care has been less pronounced because of differences from the medical care systems in some Western countries. However, it is now impossible to avoid this issue in light of projected future medical expenditures.

Prospective, controlled intervention trials need to be performed in Japan in the future.

Conclusion

The Japanese Circulation Society has been preparing guidelines for the diagnosis and treatment of cardiovascular diseases since 1998. Through joint research in 2000–2001, "guidelines for the diagnosis and treatment of acute coronary syndrome (Study Group led by Tetsu Yamaguchi)" were prepared and published. The need for accumulated evidence in Japa-

nese patients is clear, in view of possible future revision of the guidelines.

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Progress in Percutaneous Coronary Intervention
—Prevention of restenosis using IVUS—

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Abstract: Intravascular ultrasound (IVUS) appeared at the same time as the induction of new technology in the field of coronary intervention, and both have supplemented each other in their development. IVUS, which can directly observe a cross section of the coronary artery, has contributed to the elucidation of the dilatation mechanism and restenosis mechanism related to the device, and the findings obtained have been reflected in new clinical techniques. In a comparison with the coronary angiography guide, it was found that a large lumen can be secured with a big balloon with the IVUS guide without increasing the risk of complications. The observation of the luminal area makes provisional stenting possible. In this regard, a technique called "spot stenting," involving the insertion of a stent to an insufficiently dilated site, has been devised. Though there is no special definition of optimal stenting, "bigger is better" when it comes to the stent area measurement, which is useful for the prevention of restenosis. It is essential for the DCA technique to grasp the volume and direction of the atheroma. The technique involving ablation of the plaque with the use of the IVUS guide to find its direction as accurately as possible is now a standard DCA technique. In view of the correlation of residual plaque to intimal proliferation, a debulking stent has been developed for insertion of a stent after ablation of the atheroma. As to the eluting stent that has recently been attracting attention, good apposition to the vessel wall is essential for the stent to demonstrate its effect. In this regard, the role played by IVUS is expected to become more important.

Key words: IVUS; Percutaneous coronary intervention; Restenosis
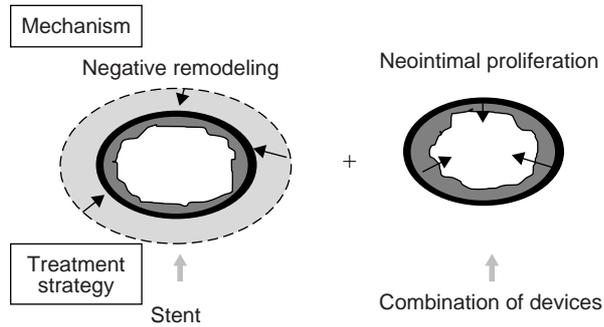
Fig. 1   Mechanism of restenosis
The proliferation of neointima and negative remodeling of vessel are the factors causing restenosis.
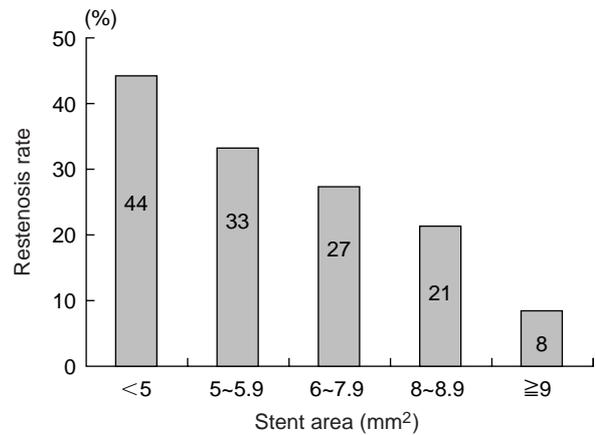
Fig. 2   Relation between stent area and restenosis rate
The concept of "bigger is better" is also applicable to stenting.

Introduction

Observation of coronary arteries was made possible in 1988 with intravascular ultrasound (IVUS). This was about ten years after the introduction of percutaneous coronary intervention (PCI), a time that corresponds with the appearance of the new devices in the field of interventional cardiology. The elucidation of dilatation form and the restenosis mechanism is essential for the development of PCI. IVUS, which allows direct observation of vascular short axis images, is ideal for this purpose. In fact, feedback from the findings obtained by IVUS was used in developing the technique and indications of PCI. PCI, and IVUS have supplemented each other in their development. The accumulation of findings related to restenosis in particular has had a great impact on the PCI technique.

Current use of IVUS in PCI

While the coronary angiography is a method to capture the silhouette of the vascular lumen, IVUS directly observes the vascular cross section. With IVUS, quantitative evaluation including the vessel size, the amount and local presence of the plaque, and the luminal size as well as qualitative evaluation including the plaque characteristics is possible. The information obtained is used for such reasons as to select a device, to determine the size and length of device, to grasp the direction of ablation and to determine the endpoint.

Mechanism of restenosis

The long-term outcomes achieved by PCI are determined by net gain (subtracting late loss from acute gain). This late stage lumen loss corresponds to the mechanism of restenosis. The loss has been considered to be attributable to the proliferation of neointima. However, investigations using IVUS clarified that the reduction of coronary vessel size (negative remodeling) is a big factor causing the late stage lumen loss (Fig. 1). The stent is a device that can prevent this negative remodeling and consequently prevent restenosis.

1. Bigger is better

As described above, the restenosis is determined by net gain. Accordingly, it is important to obtain a bigger acute gain in the initial stage. This concept, expressed as "bigger is better," is commonly applied to all devices. In fact, the follow-up results after stent treatment correlates to the stent area observed by IVUS (Fig. 2).[1,2] The final stent area and diameter are also used as factors to predict restenosis in multivariate analysis. On the other hand, neointimal
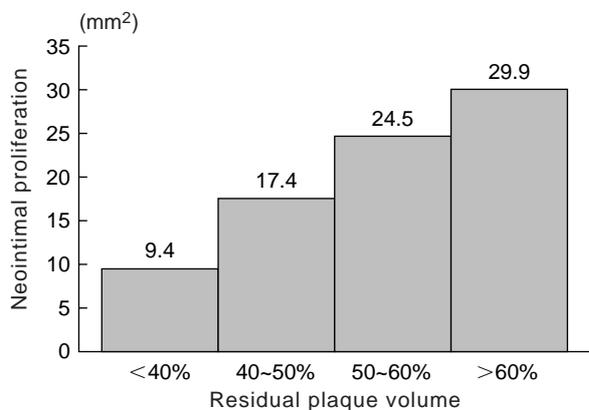
Fig. 3 Relation between the residual plaque volume outside the stent and neointimal proliferation
The result suggested that the residual plaque volume is a factor to predict restenosis.

proliferation after stent deployment is unrelated to the stent size, indicating a limit to the efficacy of stent against small vessel disease.

2. Residual plaque volume and restenosis

A report by Mintz attracted attention to the residual plaque volume as a factor to predict restenosis.[3] When the restenosis rate and residual plaque volume were investigated in the clinical studies CAVEAT, OARS, and ABACUS using DCA (directional coronary atherectomy), there was a correlation. Subsequently, Prati *et al.* reported that the degree of intimal proliferation in the stenting cases was also related to the amount of plaque outside the stent (Fig. 3).[4] Accordingly, the PCI technique to reduce the residual plaque volume is considered to decrease the restenosis rate.

Current strategies for the prevention of restenosis

1. IVUS guided balloon dilatation

As observation by IVUS can accurately assess vessel size, an appropriate balloon size can be selected, thereby improving the long-term outcomes. The CLOUT pilot trial investigated the effect of balloon dilatation using the IVUS guide. According to the results, the

observation by IVUS disclosed that a larger balloon was necessary in 73% of the lesions even though optimal results were indicated by the coronary angiography. After the size upgrade, the residual stenosis improved from $28 \pm 15\%$ to $18 \pm 14\%$ and the minimum lumen area was increased from $3.16 \pm 1.04\,\mathrm{mm}^2$ to $4.52 \pm 1.14\,\mathrm{mm}^{2}$.[5]

2. Stent

Though the stent plays a central role in PCI, it cannot completely solve the problem of restenosis. Rather, treatment against stent restenosis is causing a new clinical problem. Various stenting techniques have been investigated to prevent restenosis.

(1) Provisional stenting, spot stenting

The strategy to additionally insert a stent only when the results of balloon dilatation is suboptimal is called "provisional stenting". The IVUS guide is used in this strategy in order to select the optimal balloon size and to check for suboptimal angiographic results. The revascularization rate in provisional stenting using the IVUS guide was favorable at 8% and was reported to reduce the need for stent insertion by half. According to SIPS, provisional stenting using the IVUS guide contributed better to long-term outcomes in comparison with the coronary angiography guide.[6]

Spot stenting is an extrapolation of provisional stenting. Columbo *et al.* proposed the usefulness of a therapeutic technique to treat diffuse lesions using the IVUS guide and to conduct spot stenting in insufficiently dilatated sites.[7]

(2) Optimal stenting using the IVUS guide

The concept of optimal stenting was generated to prevent thrombotic occlusion of the stent. However, favorable stent expansion, attributable to high pressure, and administration of a strong anti-platelet drug have solved this problem. Accordingly, the investigation is focused on optimal stenting from the viewpoint of restenosis prevention.

However, there is no definite criteria for the
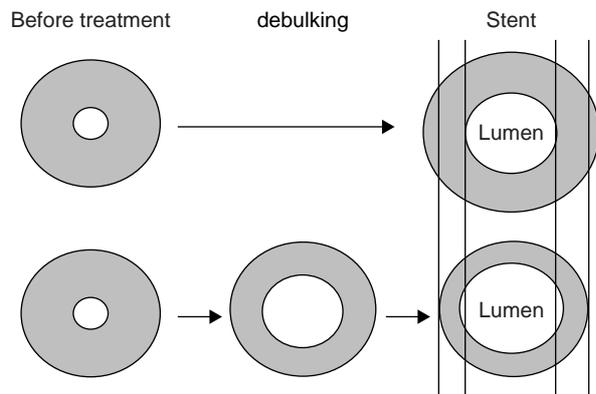
Fig. 4 Concept of debulking stent
The basic concept is to reduce the plaque volume, to minimize the vessel stretch, and to obtain a larger stent area.

Table 1 Factors to Predict Restenosis of Stenting Subsequent to Rotablator

Target lesion revascularization	IVUS not used		IVUS used	
	8/23 (35%)		26/128 (20.3%)	
	Odds ratio	P value	95%Cl	
Quantitative coronary angiography factor; Lesion length	1.08	0.02	1.01~1.15	
IVUS factor; Lesion length Final stent area	1.07 0.51	0.04 0.01	1.0~1.15 0.31~0.85	

endpoint of IVUS in stent insertion. In this regard, no definite conclusion was obtained as to the usefulness of IVUS in restenosis prevention in multicenter comparative studies (CRUISE, OPTICUS, AVID) that compared the stent insertion using the coronary angiography guide with that using the IVUS guide.[8,9] Accordingly, in the case of simple lesions indicated for a clinical study, the stent implantation to reduce the residual stenosis to 10% or less by high pressure stent expansion without the IVUS guide is expected to achieve a result comparable to that obtained by stent insertion using the IVUS guide.

On the other hand, the superiority of the IVUS guide was demonstrated in each clinical study involving various factors such as the minimum lumen diameter and residual stenosis. Accordingly, the stent insertion using the IVUS guide is considered valid against complicated lesions and high risk lesions.

It is noteworthy that about 30% of the cases did not clear the endpoint in OPTICUS.[8] The result reflected that insufficient expansion of stent is a big factor in causing stent restenosis.

(3) **Debulking-stent**

Debulking-stent is a technique that combines the ablation of plaque by DCA or rotablator with stent insertion. The basic concept of this strategy is to decrease the restenosis rate by reducing the residual plaque volume by ablation, by minimizing the stretch of vessel, thereby obtaining a larger stent area (Fig. 4). Moussa *et al.* compared the stent insertion after DCA with conventional stenting method, and reported that the acute lumen gain was significantly larger and the late lumen loss was significantly smaller in the former case.[10]

Concerning the combination of rotablator and stent insertion, there is a limit to the rotablator burr size. In this regard, the technique is aimed at favorable stent expansion by lesion modification rather than favorable ablation effect. Table 1 shows the factors to predict restenosis in cases treated at our institute. The stent was inserted in these cases subsequent to a rotablator against calcified lesions. The contents of Table 1 convince us again that the stent area is a factor in predicting restenosis and that "bigger is better" is the basic concept for restenosis prevention even in the case of debulking-stent.

3. DCA

According to the results of clinical studies CAVEAT and CCAT of DCA conducted in the initial stage, there was no difference in the restenosis rate between the balloon dilatation cases and DCA cases. Rather than that, the increase in creatine kinase was observed more frequently in the cases treated with DCA.
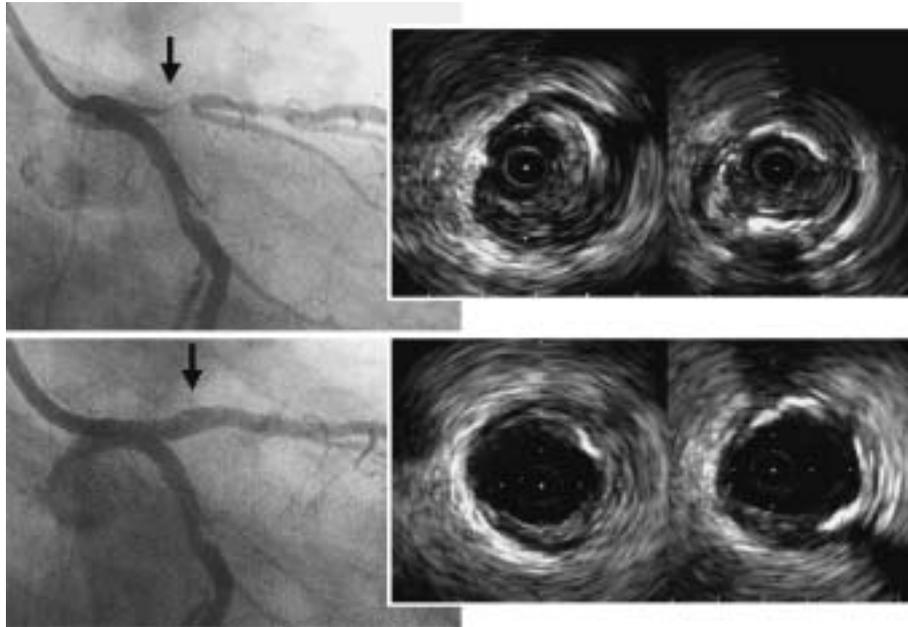
Fig. 5   DCA using the IVUS guide
Top rows: Before DCA   Bottom rows: Optimal DCA using the IVUS guide
A technique to ablate plaque as much as possible while grasping the direction of plaque using the IVUS guide

However, the high restenosis rate in the DCA group in these studies was assumed to be attributable to a problem in the technique of DCA. As a result, the optimal DCA to reduce the residual plaque volume is now considered ideal. In fact, the BOAT study conducted to verify the therapeutic effect of DCA to more aggressively ablate the plaque indicated that the restenosis rate could be decreased by DCA.

At present, the technique to ablate plaque as much as possible while grasping the direction of plaque using the IVUS guide is accepted as a standard technique (Fig. 5).

Conclusion

Current IVUS usage is described above from the viewpoint of restenosis prevention. As to the eluting stent that has recently been attracting attention, good apposition to the vessel wall is essential for the stent to demonstrate its effect. In this regard, the role played by IVUS is expected to become more important.

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Changing Clinical Aspects of Ischemic Heart Disease in Japan

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Abstract: Because of recent advances in medication and revascularization techniques, the clinical prognosis of ischemic heart disease (IHD) patients has markedly improved. The increase in the Japanese population following a Western lifestyle has been associated with an increase in IHD, particularly in the younger population ($<$50 years). In addition, the number of very old IHD patients who survive other medical illness is also increasing. The increase in IHD the younger population is associated with an increase in the metabolic disorder (obesity, hypertension, hyperlipidemia, and impaired glucose tolerance). Between 1980 and 1990, the mean total cholesterol level of the Japanese general population ($\geq$30 years) increased from 186 to 199 mg/dl in men and from 191 to 207 mg/dl in women. This increase was particularly marked in the younger population of both genders. Diabetes mellitus is also increasing steeply in Japan, and approximately 6,900,000 persons had diabetes in 1998. The prevalence of smoking has decreased, except in younger women, but it is still a problem, with high smoking rates of 55% among men and 13% among women in 1998.

Key words: Ischemic heart disease; Clinical picture; Coronary risk factor

Introduction

The development of new drugs and advances in revascularization techniques have resulted in dramatic improvements in the treatment of ischemic heart disease. However, the incidence of ischemic heart disease in Japan has continued to increase, without showing any tendency to reduce. This can perhaps be explained by the marked changes in the lifestyles and dietary patterns of the Japanese people.

The Incidence and Mortality Rate of Ischemic Heart Disease[1]

Over the past 40 years, the mortality from heart disease in Japan has been broadly flat, or slightly on the decrease. The mortality from ischemic heart disease (IHD), the predominant heart disease encountered in clinical practice, increased until 1970, but thereafter has shown a slow downward trend. This tendency is in sharp contrast to that of cerebrovascular disease, the
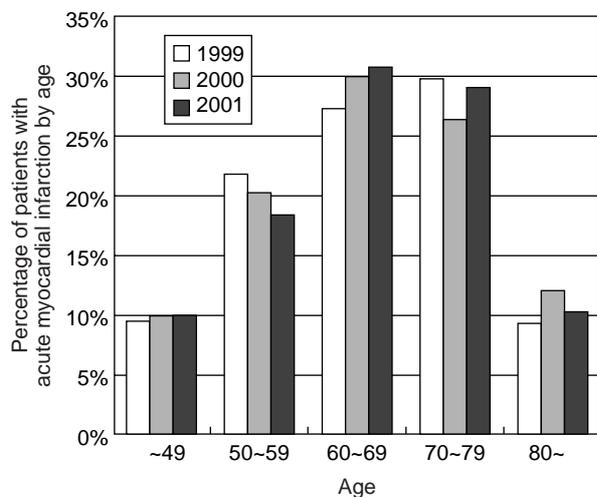
Fig. 1 Age distribution over time of patients with acute myocardial infarction admitted to the Department of Cardiology, Jichi Medical School Hospital

mortality from which had decreased to one-third during the same period.

Heart disease is the third leading cause of death in our country. Acute myocardial infarction (MI) accounts for over half of the deaths from heart disease. In 1997, the mortality from MI was estimated to be 46.6 per 100,000 in men, and 42.3 per 100,000 in women. However, advances in diagnostic and therapeutic methods have brought about remarkable improvement in the prognosis of MI in the acute phase.

The incidence of MI or sudden death did not show any significant changes from the 1960's to the late 1980's, based on a survey conducted by the epidemiological study group appointed by the Ministry of Health and Welfare (now reorganized as the Ministry of Health, Labour and Welfare). The age-adjusted prevalence of MI has, however, been on the decline since the 1980's. Notwithstanding, with the aging of society, the number of patients with MI has actually been increasing.

The average age of patients with MI is 62 to 65 years in men, and 70 to 74 years in women. Thus, the average age at onset of MI is about 10 years higher in women than in men. This state-

ment also holds true for the incidence of MI in the United States and Western Europe.

The incidence of MI has been increasing in both relatively young people and in the elderly. For instance, a study of the age distribution of patients with AMI who were admitted to the Department of Cardiology, Jichi Medical School, showed that the number of inpatients with AMI or unstable angina increased steadily, although not significantly, over the previous three years among subjects under 50 years of age, as well as among those over 80 years of age (Fig. 1).

The increasing incidence of MI and other ischemic heart diseases in the younger generation may be related to rapid progression of coronary arteriosclerosis in this subject population. This assumption is supported by many studies. An epidemiological study demonstrated that the mean serum cholesterol level in the younger population increased by 10 mg from 1980 to 1990.[2] An autopsy study of subjects 1 to 39 years of age revealed that the extent of coronary arteriosclerosis was significantly increased in males in their twenties and thirties between 1991 to 1995 than between 1978 to 1982. Another study reported that the incidence of arteriosclerosis was similar in pediatric subjects 15 years of age in Japan and the United States. In subjects older than 15 years, arteriosclerotic changes were more marked in Japanese than in American subjects.[3]

Features of Ischemic Heart Disease in the Elderly Population

Elderly people have been generally defined as those 65 years of age or older in many studies, but a recent survey indicated that there is a common tendency for only people well over 65 years of age to be called elderly. Regardless of the definition considered, which may vary among studies, the features of ischemic heart disease common to the elderly are as follows:
1) Myocardial ischemia is frequently

asymptomatic.

2) A relatively greater proportion of elderly patients with ischemic heart disease have multivascular disease or history of previous MI. Furthermore, in this patient population, heart pump dysfunction or cardiac rupture is more likely to occur as a complication, and the prognosis is often worse.

3) Many elderly patients with ischemic heart disease have concomitant disease, including cerebrovascular disease, restlessness, renal dysfunction, pneumonia, and other organ dysfunctions. In-hospital death among such elderly is also considerably high.

Age is an important risk factor for ischemic heart disease in the elderly. Smoking is thought to be associated with multivascular disease. Comorbidity is frequently observed in elderly patients. The prevalence of hypertension, hyperlipidemia, and diabetes mellitus in this patient population is relatively high. The ratio of females among patients with IHD increases with advancing age of the patients. The prognosis in IHD is significantly dependent on the age of the patient. The more advanced the age, the higher the rate of in-hospital mortality.

According to a research group formed by the Longevity Science Organization, early detection of ischemic heart disease is generally difficult in elderly patients. Their symptoms may be atypical, which may result in missed diagnosis and delayed treatment. Furthermore, the use of catheters during diagnostic procedures frequently causes problems in elderly patients. These factors have contributed to increase in the overall mortality (16.8%) and cardiac death (12.4%), by roughly about 5 times that noted in middle-aged group. One report also pointed out that cardiac death was primarily due to congestive heart failure or heart rupture in the elderly, while in middle-aged patients, cardiogenic shock was the predominant cause of cardiac death.

Changes in Coronary Risk Factors

The incidence of metabolic disorders, such as obesity, hyperlipidemia, and abnormal glucose tolerance has been rapidly increasing in recent years. Preventive measures for these disorders should be instituted in combination with counseling for smoking cessation and blood pressure control. The increased incidence of metabolic diseases has been associated with an increased incidence of ischemic heart disease, especially of MI and severe three-vessel disease. Treatment results and mortality rates in patients with ischemic heart disease have reached levels similar to those in the United States and Western Europe. However, while the incidence of ischemic heart disease has been decreasing in these developed countries as a result of efforts directed at improving lifestyles and advances in therapeutic methods, the incidence curve in Japan remains flat or even increasing.

1. Sex

The incidence of cardiovascular disease is very low in females in their early forties or younger; however, the incidence shows an upward trend in women in their late 40's and 50's, i.e., during menopause, and reaches a level similar to that in men in women in their late 60's. A cohort study on Hisayama-machi residents[4] showed that this tendency has not significantly changed among the three time-periods studied, namely, 1962 to 1970, 1971 to 1979, and 1980 to 1988.

2. Hyperlipidemia

A basic survey of cardiovascular disease by the Ministry of Health and Welfare[5] showed that the serum total cholesterol level (TCL) in males aged 30 years or older increased from 186 to 199 mg/dl during the 10 years from 1980 to 1990, while in females aged 30 years or older, during the same period, the level changed from 191 to 207 mg/dl. The proportion of subjects with serum TCL equal to 220 mg/dl or over

was the largest in subjects in their forties (31.1%) among males and in subjects in their sixties (52.6%) among females. The proportion of people with the specified TCL or over has continued to increase gradually. The average serum TCL has also increased after 1990, especially in younger people.

Elevated TCL is associated with a higher incidence of ischemic heart disease. The risk in males with a serum TCL of 200 is 1.7 to 2.0, relative to those whose TCL is 160 to 170. When the TCL level increases to 220 or over, the risk ratio jumps to 2 to 5 relative to those with a TCL of 160 to 170. The risk ratios are similar for females. HMG-CoA reductase inhibitors, which were introduced into clinical practice as anti-hyperlipidemic agents in the 1990's, have been confirmed to effect a decrease in the incidence and mortality rate of MI.

3. Hypertension

The average blood pressure is known to be correlated with the incidence of coronary artery disease. The Hisayama-machi cohort study showed that the systolic blood pressure level was related to the incidence of coronary arteriosclerosis, but the incidence of coronary artery disease had not changed over time.

The prevalence of severe hypertension has decreased, while the number of patients with mild diastolic hypertension or borderline hypertension has been on the increase. The average systolic blood pressure has shown a continued tendency to decrease in both males and females since 1961.

4. Diabetes mellitus

The prevalence of diabetes mellitus has been increasing year by year. According to the 1998 epidemiological survey, the number of diabetic patients was estimated to be approximately 6.9 million. This may be attributable to genetic disposition and changes in lifestyles. Excessive fat intake due to adoption of westernized diet patterns and physical inactivity have led to an increased incidence of obesity.

The incidence of the first episode of ischemic heart disease in diabetic patients is as high as the recurrence rate in non-diabetic patients with previous MI. The relative risk of MI is greater than 2.0 in diabetic patients in Japan.[6]

5. Overweight

The Framingham Study has reported that obesity was a risk factor for ischemic heart disease, independent of smoking, serum total cholesterol level, systolic blood pressure, impaired glucose tolerance, and hypercardia.[7] A tendency towards increase in the number of obese subjects has been observed in our country. Impaired glucose tolerance, hyperlipidemia, and hypertension are strongly related to obesity, especially to abdominal fat obesity.

6. Cigarette smoking

Cigarette smoking has been confirmed to be associated with both increased morbidity rate and mortality rate from ischemic heart disease. The number of pack years of cigarette smoking is strongly correlated with the risk of coronary artery disease. The relative risk of smokers to non-smokers is 1.73 for males and 1.90 for females. Although the number of smokers has been gradually decreasing, the percentage of smokers is still remarkably high in Japan as compared to that in the United States and Western Europe. The smoking rates among Japanese males reached its peak (83.7%) in 1966, and subsequently showed a downward trend, decreasing to 55.2% in 1998. The smoking rate among females has, however, remained unchanged (13.3%) during the same period. The absence of reduction in the smoking rate in young female smokers in their twenties and thirties is a matter of particular concern, since this would be expected to result in a higher incidence of ischemic heart disease in the future.

Advances in the Treatment of Ischemic Heart Disease

Advances in the treatment and diagnostic methods of ischemic heart disease have brought about marked improvement in the prognosis of MI in the acute phase. Such advances include the establishment of coronary care units (CCUs) in many medical institutions throughout the country, earlier reperfusion therapy, strategic drug therapy using β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARB). In particular, earlier revascularization has greatly contributed to reduction in the incidence of cardiac rupture and inhibition of prolonged myocardial remodeling, which has resulted in much improved prognosis in a large number of patients with ischemic heart disease.

Mechanical assist devices, such as intraaortic balloon pumping (IABP) and percutaneous cardiopulmonary support (PCPS) have also been confirmed to be effective in improving the survival rate in cases of acute MI. In addition, risk factor monitoring and secondary prevention by medication (using statins, ARB, ACE inhibitors, and antithrombotic agents) have also played a role in improving the prognosis of MI.

MI is often accompanied by heart failure (15 to 27%), cardiogenic shock (15 to 18%), and cardiac rupture (4 to 5%). The mortality rate among MI patients with these complications is high both in Japan and in Western countries.

In-hospital mortality from AMI was estimated to be 29% in the 1960's, 21% in the 1970's, 16% in the 1980's, and 10% in the 1990's in the United States and Western Europe. In Japan, the mortality was calculated to be 30.5% from 1982 to 1985, when CCUs were scarcely established in medical institutions, but decreased to 9.4% after CCUs became a commonplace. Percutaneous transluminal coronary angioplasty (PTCA) and percutaneous transluminal coronary recanalization (PTCR) have been shown to reduce the incidence of for-
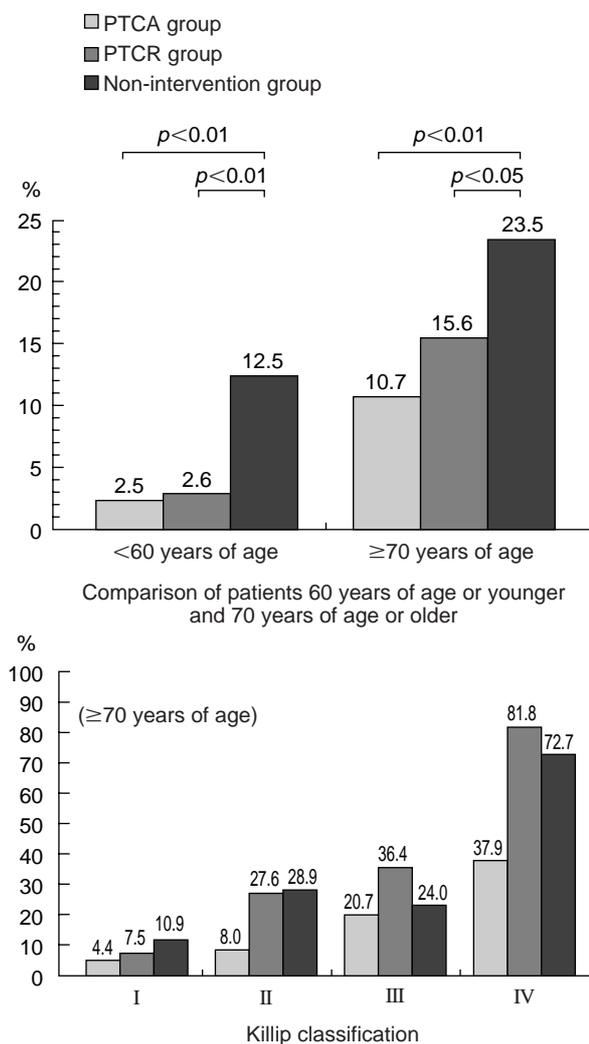
Fig. 2 In-hospital mortality among patients with myocardial infarction by intervention. (excerpt from *Japanese Circulation Journal of the Japanese Circulation Society* 1998; 6(1): 5–10)

mation of ventricular aneurysm. In-hospital mortality from AMI at the Department of Cardiology, Jichi Medical School Hospital was 4.7 % in 2001, and the mortality even among patients with acute MI classified as Killip class IV decreased to the 40% range.

Despite advances in the methods of treatment of ischemic heart disease, the short-term prognostic factors nonetheless remain old age, female sex, previous history of hypertension, diabetes mellitus, or MI, Killip class III or more advanced, and no reperfusion therapy. These

risk factors still significantly increase the mortality rate (See Fig. 2. Mortality rate by Killip classification stage).

Concerning the long-term prognosis, death rates after one year, three years, and five years after an episode of MI were 6.2%, 7.6 to 12%, and 18 to 19.1%, respectively in Japan. In Western countries, the corresponding rates were 8 to 14.1%, 14 to 33%, and 19 to 39%, respectively, which indicate that the prognosis is better in Japan than in Western countries. This difference is probably attributable to the preference for low fat diet and low rates of previous multivessel disease or MI among Japanese subjects. Improvements in survival rates after MI have, however, produced an increase in the number of patients at higher risk who are older, have more severe multivessel disease and more severe cardiac dysfunction. This may complicate the clinical picture of ischemic heart disease further in the future.

Conclusion

Change in the lifestyles of Japanese people has resulted in an increased incidence of ischemic heart disease in both the younger generation and in the elderly. The ever-increasing number of ischemic heart disease patients among relatively younger people highlights the importance of management of patients at higher risk of coronary artery disease and primary preventive measures. Furthermore, the increase in the incidence of ischemic heart disease in the high-risk elderly population also points to the importance of effective treatment and management of these patients so as to maintain the quality of life and avoid a bedridden life in these patients.

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Depression and Cardiovascular Disease

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Abstract: Depressive disorder occurs frequently in response to the onset of several cardiovascular diseases, particularly in the post-myocardial infarction period, and can become an important determinant of prognosis or recovery. In patients whose heart disease or hypertension is managed by a cardiologist or primary care physician, depressive disorder is apt to go undiagnosed and therefore untreated. The Self-rating Depression Scale (SDS) and∕or Mini-International Neuropsychiatric Interview (MINI) have been proposed as simple, useful diagnostic questionnaires for use in such patients. In the relationship between depressive disorder and cardiovascular diseases, the "physical or mental exhaustion" that can occur under depression seems to bear a great deal of responsibility for the onset or prognosis of cardiovascular diseases, because the pathophysiological features of depressive disorder closely resemble those of an exhausted human or animal. Selective serotonin reuptake inhibitors (SSRIs) appear to be a safe form of treatment for depressive disorder, especially in patients with preexisting cardiovascular diseases. However, the prevention of depressive disorder might be even more important, by preventing patients from falling into the exhausted state.

Key words: Depressive disorder;
Heart disease∕hypertension (cardiovascular disease);
Selye's stress theory; Selective serotonin reuptake inhibitor (SSRI)

Introduction

In recent years, major and minor depression has been cited as a risk factor for heart diseases such as myocardial infarction. It has also attracted attention as the cause of white-coat hypertension and the white-coat effect found among hypertensive patients on therapy, thereby directing attention to the relation between depression and various cardiovascular diseases.

This points to the importance of addressing depressive disorder in patients with cardiovascular diseases, even among primary care physicians and cardiologists, who generally are not trained in psychiatry.

The need to deal with depressive disorder in

the clinical treatment of patients with cardio-vascular diseases is also important for the following reasons. First, most patients in Japan with depressive disorder (80% of mild cases in particular) visit non-psychiatric departments, e.g., departments of general internal medicine or cardiology, complaining of physical symptoms. Second, 15% of patients with depressive disorder have considered suicide.

It should always be considered, particularly in cases of life-threatening cardiac or other diseases, that having the disease itself may cause a depressed mood or induce depression.

This paper describes the importance of addressing depressive disorder in the clinical treatment of heart diseases and hypertension and examines treatment options.

Relation between Heart Disease or Hypertension and Depressive Disorder

It is apparent from a number of reports that depression has a great influence on the development, course, and prognosis of heart disease and hypertension.[1–4] It has also been documented that myocardial infarction occurs frequently among patients with depressive disorder, and that the incidence of depression and the mortality of patients with depressive disorder are high after the onset of myocardial infarction.

Schleifer et al.[1] have reported that major or minor depression occurring 8–10 days after the onset of myocardial infarction was found in 45% of patients as a whole. Alpert and Rippe[3] noted that CCU patients with myocardial infarction often manifest a depressive state, depending on the speech, behavior, and attitude of the care staff and the CCU environment, as well as on the type of disease, and pointed out the importance of taking into account the patient's mental status. They also reported that depression persisted after the patient's release from hospital, a condition referred to as "homecoming depression," and advocated active support by a medical care team and encouragement of patients' participation in social activities.

Depression and lack of social engagement following the onset of myocardial infarction are known to be associated with increased mortality. According to Frassure-Smith,[2] among 222 patients with myocardial infarction, mortality at 6 months was markedly higher in those who remained in a depressive state after onset (17%) than in those without depression.

On the other hand, a number of reports have documented that myocardial infarction, arrhythmia, and sudden death occur at high frequencies in patients with depressive disorder.[4,5] Furberg et al. of the Cardiovascular Health Study Collaborative Research Group reported on 4,493 persons of advanced age who had no cardiovascular disease and were followed for 6 years. They found that, the higher the mean depression score, the higher the incidence of heart disease. In addition, Engel[5] analyzed many patients in whom sudden death occurred possibly because of psychological stress. He found among these patients many cases of sudden death occurring probably under a depressive state caused by a sad event or severely damaged self-esteem, and presumed that the deaths were caused by arrhythmia. Thus, dealing with depression is important both from the aspect of the prevention of heart disease and from that of treatment and control.

The importance of attention to major and minor depression in terms of their relation to hypertension has also been widely noted. Patients with depression or anxiety are frequently hypertensive. In this context, an important issue is white-coat hypertension in depressed patients and a white-coat effect on blood pressure in hypertensive patients on antihypertensive drug therapy. If antihypertensive drug therapy is initiated or increased only on the basis of blood pressure readings obtained in a doctor's office or clinic in patients with unstable blood pressure under a depressive state, organs such as the brain, heart, and kidneys may be harmed, a result that would be

antithetical to the true purpose of antihypertensive therapy. Therefore, comparisons with home blood pressure and 24-h ambulatory blood pressure monitoring are important.

Another issue is that the depressive state causes decreased blood flow in organs, resulting in injury to the brain, heart, and kidneys. Therefore, organ deterioration in depressive patients on antihypertensive therapy, especially with excessive dosis or inadequate antihypertensive drug, must be prevented.

In addition, the depressive state is associated with decreased physical activity and increased drinking and smoking, i.e., failure to carry out lifestyle modifications prescribed in guidelines for the treatment of hypertension. The prevention of depression is also important in this regard.

Mechanism of Depression as a Risk Factor for Heart Disease and Hypertension: Biological Reactions under Stress

Various hypotheses have been put forth as to the mechanism by which depression acts as a risk factor for heart disease and hypertension.[2,4] Among these are 1) involvement of the sympathetic and parasympathetic activity; 2) changes in platelet function; 3) injury to vascular endothelial cells; 4) vascular occlusion owing to plaque formation; and 5) increase in free radicals and fatty acids.[2,4] Apart from these hypotheses, one factor to be noted is that most animal models of depression used in experimental studies or in the development of antidepressant drugs employ small animals that have undergone continuous stress loading (exhausted animals). This is done because specific features of an exhausted animal, e.g., serotonin and catecholamine metabolism and various biological functions, are considered to closely resemble those of depression in humans. This suggests that the exhausted condition resembles depression in humans as well as in animals.
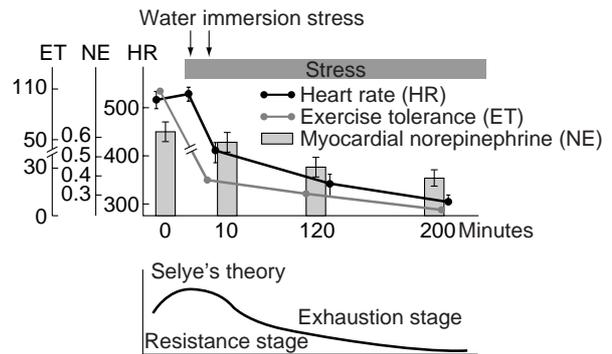
Fig. 1 Changes in heart beat rate, myocardial norepinephrine, and exercise tolerance in rats under continuous stress

It is important here to refer to Selye's stress theory,[6] which is useful for considering the process, mechanisms, and biological reactions of an individual under stress who lapses into a depressive state.

According to Selye's theory, when stress is imposed, the living body exhibits the following three reactive phases as stress persists.[6]

1. Reactions in the alarm stage: In the initial stage of stress stimulation, the body does not respond to the stimulation because it is not ready to do so, or if the stimulation is strong, it may exhibit decreased vital functions, i.e., decreases in blood pressure, body temperature, and blood glucose levels, in some cases, resulting in a state of shock.

2. Reactions in the resistance stage: Subsequent reactions include blood pressure elevation, increased heart beat rate, and enhancement of blood circulation (decreases in blood flow in organs may occur due to peripheral vasoconstriction), all of which are commonly called stress reactions.

3. Reactions in the exhaustion stage: If stress persists for a prolonged period, the body will become exhausted, and thus exhibit deteriorated functions. Figure 1 shows the results of our previous experiment on stress loading in rats. When stress stimulation persisted, the heart rate and myocardial norepinephrine level continued to decrease over time, while exercise

Table 1   Suppression of Immune Function by Stress

Description of stressor	Immune function	Publication	
Psychosocial problems	Increased morbidity of upper respiratory tract infection	1962	Jacob
Chronic stress in living	Decreased resistance to hemolytic streptococcal infection	1962	Meyer
Sleep disturbance	Decreased phagocytotic activity against hemolytic streptococci	1976	Palmbland
	Decreased interferon production		
Spouse's death	Decreased T cell function	1977	Bartrop
Qualifying examination	Decreased lymphocyte response to PHA	1982	Dorlan
Anxiety and depressive response to changes in living	Decreased NK cell activity	1983	Gottschalk
Spouse's death	Decreased lymphocyte response to PHA and PWA	1983	Schleifer
Advanced age without social support	Decreased lymphocyte response to PHA	1985	Thomas
Depressive disorder	Decreased lymphocyte response	1986	Kronfol
Psychological stress	Increased morbidity of common cold virus infection	1991	Cohen
Experience of loss, interpersonal stress	Increased frequency of recurrent labial herpes	1991	Schmidt
Natural disaster (e.g., hurricane)	Decreased NK cell activity	1997	Ironson

(Adapted from Kubo, C.: *Stress and Rinsho* 1999; 1: 20)

tolerance also showed a prominent decline.[6] Sudden death and heart disease or various other diseases can occur in this state of exhaustion.[3,5] We previously investigated the life situation during one week before onset in patients with myocardial infarction who were treated in CCU. About half of the patients were exhausted by the stressors of work or domestic affairs and developed the infarct under a situation similar to that of the depressive state, e.g., complaining of inability to sleep. Kubo at Kyushu University enumerated decreases in immunological function under various types of stress, as shown in Table 1.[7] These stressors often corresponded to those of the exhaustion stage of chronic stress. Decreased immunological function in the exhaustion stage or in a depressive state seems to greatly affect the course and prognosis of illness.

Thus, when they are exhausted owing to conditions of continuous stress, humans, as well as animals, show deteriorated biological functions and declines in behavior and volition, similar to the clinical symptoms of major and minor depression. Therefore, one of the basic factors in controlling depression seems to be that of preventing patients from being mentally and physically exhausted from stress.

Overview of the Diagnosis of Depression in Clinical Cases of Cardiovascular Disease

Patients with major or minor depression generally present mental and physical symptoms such as those listed in Table 2. In the clinical setting, depressive state is often recognized by its characteristic features, including melancholic mood, decreased ability to think and act, sleep disturbance, and sickness in the morning that improves by evening.

The psychiatric diagnosis of depression is based on established criteria such as those of the DSM-IV or ICD-10. However, these criteria are complicated and unfamiliar to primary care physicians and cardiologists, who are not specialists in psychiatry.

Therefore, a self-rating depression scale (SDS) consisting of 20 items has long been used as a simple method of diagnosing depression, particularly in mild cases. In addition, an even simpler diagnostic tool, the Mini-International

Neuropsychiatric Interview (MINI) has been available since 1998.[8]

The MINI consists of a group of simple questions beginning with those to determine whether the subject has been feeling unhappy much of the time and whether he or she has lost interest in various things.

Most patients with depressive disorder who attend the department of internal medicine or cardiology seem to have mild psychogenic disease owing to extreme psychosomatic wasting. Therefore, it is important to make good use of SDS and MINI so as not to overlook mild depression.

Treatment of Depression and SSRIs

1. Drug treatment

Although tricyclic and tetracyclic antidepressant drugs have been widely used for some time, in recent years, selective serotonin reuptake inhibitors (SSRIs), which are associated with fewer side effects and thus easier to use, have been developed and become commonly used.[9,10]

Tricyclic antidepressant drugs are known to have certain side effects, such as those derived from their anticholinergic action (thirst, urinary disturbance, constipation) and α_1 block-

Table 2 Clinical Features of Depressive Disorder

Physical symptoms

- A variety of physical symptoms (anorexia, malaise, etc.)
- Sleep disturbance

Mental symptoms

Emotion	Depressive mood (feeling gloomy) Pessimism Anxiety, irritability
Volition, behavior	Lack of concentration Decreased perseverance Decreased speech and behavior
Thought	Suspension of thinking, decreased ability to judge
Others	Self-reproach, suicidal ideation

Others

- Symptoms show circadian variations (worse in the morning and better in the evening).
- Antidepressant drugs are effective.

Fig. 2 Pharmacological features of selective serotonin reuptake inhibitors (SSRIs)
(Comparison with tricyclic antidepressants)

ade (dizziness, feeling lightheaded on standing up), as well as side effects on the cardiac conduction system and cardiac rhythm.[3] On the other hand, tetracyclic antidepressant drugs, which appeared in the 1980s, are known to cause fatigability and sleepiness because of their antihistaminic action.[3] Therefore, tricyclic and tetracyclic antidepressant drugs have been difficult for primary care physicians and cardiologists to use in patients with heart disease. In this regard, the recently developed SSRIs such as fluvoxamine and paroxetine heighten the decreased activity of the serotonin system to exert an antidepressant effect, while presenting fewer side effects related to anticholinergic, antihistaminic, and adrenalin α_1 blocking actions than tricyclic and tetracyclic antidepressants (Fig. 2). They also have hardly any cardiac toxicity. In addition, SSRIs prevent myocardial infarction through their inhibition of platelet function.[9] In a double-blind comparative study with a tricyclic antidepressant drug in patients with myocardial infarction who had concomitant depressive disorder, discontinuance of therapy owing to the development of arrhythmia or other adverse reactions was markedly less frequent with SSRI therapy.[10] Thus, SSRIs are regarded as easier to use for patients who have depression and heart disease.

2. Psychotherapy

Brief psychotherapy and counseling can be implemented by primary care physicians. Relevant monographs should be referred to for details.

3. Life style modification

(1) Patients should be encouraged to rest, find enjoyable activities, sleep soundly, and engage in light exercise that does not make them too tired, in order to prevent depression from exhaustion and anxiety about disease and the stress of daily life. Analysis of their life histories is indispensable to determine what has caused the depressive state.

(2) A healthy, robust body capable of withstanding stress is important. In this regard, patients should be instructed in how to reduce risk factors and how to maintain a healthy body.

Conclusion

This communication has examined the significance of depressive disorder and procedures for dealing with it when treating patients with heart disease or hypertension. It is strongly recommended that physicians pay attention to the psychological status of the patients with heart disease or hypertension in order not to overlook mild cases of depressive disorder.

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