Department of Radiology

Outline and Research Objectives

Department of Radiology was established in 1932. Our department covers three major fields that are, diagnostic radiology (imaging and intervention), radiation oncology (radiotherapy) and nuclear medicine. Research activities of radiology are being carried out in cooperation with department of clinical radiology of the University of Tokyo Hospital and with department of radiology of the institute of medical science (IMS), the University of Tokyo.

Research Objectives

Diagnostic Radiology

To develop new techniques in data acquisition of CT and MRI
To clarify pathologic background of radiological findings.
To develop new system for interventional procedures.

Radiation oncology

To develop high precision radiotherapy system
To improve radiotherapy planning.
To clarify biological mechanisms of radiotherapy from molecular viewpoints.

Nuclear Medicine

To develop new techniques and radiotracers in functional imaging.
To improve image quality and quantitative accuracy in radiotracer imaging

Faculties and Students

Professor and Chair
Kuni Ohtomo MD (diagnostic radiology 1998-)
Associate Professors
Manabu Minami MD (diagnostic radiology 1999-)
Shigeki Aoki MD (diagnostic radiology 2000-)
Keiichi Nakagawa MD (radiation oncology 2002-)
Kohki Yoshikawa MD (diagnostic radiology 1997-) (IMS)
Lecturers
Toshimitsu Momose MD (nuclear medicine 1999-)
Osamu Abe MD (diagnostic radiology 2000-)
Naoto Hayashi MD (diagnostic radiology 2000-)
Masao Tago MD (radiation oncology 2001-)
Yoshitaka Masutani ED (computer science 2002-)
Yusuke Inoue MD (nuclear medicine 1999-) (IMS)
Associates 9
Postdoctoral Fellow 1
Graduate Students 14
Residents.....6
Secretaries.....9

Past Research and Major Accomplishments

Diagnostic Radiology

1. Visualization of cerebral arteries by contrast-enhanced CT and MRI with special attention to separate between the lumen and the wall. (select publications 1-7,12)

We have revealed that dynamic contrast enhanced CT and MRI can be used to visualize vascular lumen as well as its wall.

We developed 3D-CT angiography for cerebral arteries to visualize lumen of the arteries and aneurysms. We developed a new MR angiographic technique, named "MRDSA" which can show the hemodynamics with a frame rate of subsecond. We also established the technique to see the wall of the intracranial arteries, using contrast-enhanced MR with suppression of the luminal signal by presaturation pulse. We used this technique to see the irradiated intracranial arterial wall, which sometimes show marked enhancement. We then established the way to see the dynamic contrast changes of the wall itself.

In addition to diagnosis, we performed fundamental studies of MR-guided intravascular procedures.

2. Temporal Changes of the Apparent Diffusion Coefficients (ADCs) of Water and Metabolites in Rats with Hemispheric Infarction. (select publication 15)

The purpose was to clarify the temporal changes of ADCs of cerebral metabolites during early focal ischemia. in order to assess the pathophysiology of the reduction in diffusion properties observed both in the ischemic hemisphere and in the contralateral hemisphere.

3. Fully-Automated Segmentation of Colonic Walls and Pulmonary Vessels (select publications 19-20)

We developed new segmentation methods, which are applicable in both visualization of the colon and computer-aided diagnosis in the detection of polyps in CT colonoscopy. A new method for automated segmentation of the pulmonary vascular tree in spiral CT angiography was developed based on 3D image analysis techniques and anatomic knowledge. The results are able to be applied in detection of pulmonary embolism by limiting search area of thrombi.

4. Radiologic –pathologic correlation of various diseases (select publications 8-1116.18.21-26)

In the study the images with high spatial and contrast resolution are compared with the pathologic findings and this kind of information is helpful for differential diagnosis of diseases. This approach has been successful in the field of the CNS, liver, and ovaries.

5. New virtual CT endoscopy software

To overcome some of the disadvantages of virtual endoscopy, new software called computed sectional probe (CSP) method has been developed. This software can be applied to the diagnosis of the gastrointestinal tract and tracheobronchial tree with improved detectability and more accurate tumor staging.

Radiation Oncology

1. Development of a comprehensive system for precise radiation therapy (select publications 27.30.)

A total system for radiation therapy composed of a linear accelerator unit with a microcomputer-controlled multileaf collimator and a CT scanner installed in the same treatment room was developed 17 years ago. It was a prototype system of the widely prevailing high precision radiotherapy system.

2. Megavoltage CT scanning with a medical accelerator (select publication 29 32)

Megavoltage CT scanner using 4 MV and 6 MV radiotherapy beam was developed. A detector system is composed of 120 pairs of Cadmium Tungstate scintillators. Although spatial resolution is limited, this system has been used to verify positioning errors and beam placement in the high precision radiation therapy.

Nuclear Medicine

1. Brain activation studies by positron emission tomography (PET) (select publications 39.40)

We investigated the following issues; (I) reproducibility of regional cerebral blood flow of resting state measured by H2O-PET;(II) effect of physiological stimulation on cerebral blood flow;(III) identification of activation areas on anatomical structures. Our data suggest that relative rCBF images and their paired subtraction are more suitable for tapping functional localization. The changes of rCBF in association cortex for more complicated tasks are, in general, smaller than those in primary cortex. PET images were taken in two different conditions: blindfolded resting state and anti-saccade. We applied these activation techniques using H2O and PET to exploring motor function and language processing of Japanese language. We investigated functional neuroanatomy of chewing.

We investigated Japanese language processing in the brain using H2O-PET. The results suggested that Kanji and Kana are processed differently.

2. Evaluation of the prognostic value of FDG-PET for rectal cancer (select publications 41)

We compared several variations of a semi-quantification method, the Standardized Uptake Values (SUV) and to determine the most appropriate parameter for the prognostic prediction and to propose the quantitative guideline of the FDG-PET. SUV2 was considered to be a good prognostic indicator for long-term prognosis of rectal cancer patients.

Current Research

Diagnostic Radiology

1. Evaluation and treatment of cerebrovascular diseases with multimodality (CT, MR, US, angiography); especially with X-ray angio-open MR system.

2. MR Diffusion Tensor Analysis and Visualization (select publications 13.14)

A new display method for tractography in diffusion tensor imaging was developed. Local reliability of diffusion tracking is evaluated based on anisotropy, and paths of tracking are displayed in colors and opacity according to tracking reliability. By using several clinical data sets of volunteers and patients, the method was validated.

3. Further clinical application of 3D data acquired by Multidetector low CT (MDCT).

3-1. 3D display of secondary lobules of the lung

MDCT can generate contiguous thin section (1.25mm) CT images of the lung at every 0.6mm under single-breath holding. 3-D data of lung parenchyma is abstracted and erosion of several pixels from the lung surface can be accomplished. The structure of the secondary pulmonary lobule is clearly seen. This information will be helpful to analyze diffuse lung diseases.

3-2. 3D display of the surface of the liver

Using multi-phase dynamic study of the liver, characteristics of enhancement in each pixel can be abstracted. If the characteristics of enhancement of the liver parenchyma are set on the time-density curve, pixels showing similar enhancement pattern will be differentiated automatically on computer. This will be utilized to define the area of the liver parenchyma and eventually the data of the area will show the appearance of the liver surface three-dimensionally. The appearance will be almost the same as the liver is observed by laparoscopy or at surgery. This computer-aided automatic process will be useful the overall evaluation of changes of the liver shape and its deformity (atrophy and hypertrophy).

Radiation Oncology

1. Molecular analysis on reproductive tissue (select publications 34.35.38)

Radiation damage and recovery from ionizing radiation are being investigated from the molecular viewpoint.

2. Development of a C-arm mounted accelerator and of Dynamic Conical Conformal Radiation therapy (Dyconic CRT)

A C-arm mounted accelerator was developed. The linac head was designed to move along the C-arm with a maximum angle of 60 degrees (from a vertical position toward the gantry). Simultaneous rotation of the gantry creates a dynamic conical irradiation technique. Dyconic CRT was developed by combining the technique with continuous motion of multi-leaf collimator (MLC). Dyconic CRT enabled the precise delivery of non-coplanar beams without rotating the table.

Nuclear Medicine

1. Comparative studies of myocardial sympathetic nerve function and striatal dopaminergic function in Parkinson's disease and its related disorders.

In all patients with parkinsonism, striatum to cerebellar (ST/CBL)Ratios were significantly reduced in FDOPA-PET. Among them, only in PD and DLBD patients, heart to mediastinum (H/M) ratios, index of myocardial sympathetic nerve function, were significantly reduced in I-123 MIBG scans. Now we are accumulating the number of patients and try to analyze the data of larger series of parkinsonian patients.

2. Correlative studies of C-11 methionine (MET) and FDG PET in the evaluation of the tumor grading of preoperative brain tumor and in the differentiation of recurrent brain tumor from radiation necrosis. For the differentiation between tumor recurrence and radiation necrosis, we are trying to decide cut-off value of both MET and FDG uptake, lesion to normal gray matter tissue count ratio (L/N).

Future Prospects

Imaging and Intervention (Diagnostic Radiology and Nuclear Medicine)

1. Neruointerventional therapy for stroke and other neurological disorders using Xray angio-MR system with monitoring diffusion/perfusion and vascular wall by MR.

2. Molecular imaging in the future

In the era of molecular medicine, molecular imaging is attracting a great deal of attention in the field of imaging science. Molecular imaging approaches the molecular basis of biological processes using imaging technology. We intend to perform researches in molecular imaging. In particular, we are planning to investigate non-invasive imaging of gene expression in living animals. We hope to contribute to developing methods for gene expression imaging and, subsequently, advancing molecular biology and molecular medicine.

3. Molecular Imaging in clinical oncology

The first point is the evaluation of angiogenesis representing activity of primary neoplasms. With advent of CT- PET system, the degree of FDG uptake will be correlated with the degree of angiogenesis. Another point is the evaluation of lymph node metastasis. New contrast materials having affinity with macrophages or tumor cells itself in the node will be available on MRI in the near future.

4. Functional imaging using CT and MRI

Functional imaging focusing on perfusion will be useful especially in the liver and kidney among the body. Another functional imaging is related to the activity of hepatocytes and Kuppfer cells of the liver using tissue-specific MR contrast agents.

5. Functional imaging using radiotracers

Measurements of endogenous neurotransmitter secretion under various physiological conditions and pharmacological manipulations. We are planning to measure the amount of endogenous dopamine release from the terminals of nigrostriatal dopaminergic neurons during executing mental tasks, drug therapy and deep brain electrical stimulation in patients with Parkinson's disease, using C-11 raclopride and PET. We are also planning to develop the new radiolabeled tracers for opiate receptors, dopamine, serotonine, GABA and glutamate receptors and transporters for the evaluation of mental functions in patients with psychiatric disorders such as panic disorder, depression and schizophrenia.

Radiation Oncology

1.Image-guided real-time high dose-rate radiotherapy:

Continuous image acquisition during the therapeutic radiation visualizes errors in target localization and motion of normal structures. In rotational conformal therapy, a separate X-ray tube mounted on the linac gantry enables real-time CT imaging of the target and surrounding organs. When the system is combined with a newly investigated extremely high dose rate X-ray source (laser X-ray source), time and spatial resolution of radiotherapy will be drastically improved. It will greatly enhance radiosurgey application.

2.Tailor-made prediction of radiation sensitivity by use of DNA array tip:

Genetic factors define the radiation sensitivity of the normal tissue. Fibroblast cultures are performed sporadically but take too long time in clinical practice. DNA array analyses of single nucleotide polymorphism (SNP) may clarity how the sensitivity is determined and contribute to the decision of indication and tailor-made dose setting for radiation therapy.

Research Grants (Department of Radiology)

The Grant for Development of Advanced Medical Practice of The Ministry of Education, Science, Sports and Culture in Japan.

1. Ohtomo K. Clinical necessity of both state-of-the art CT and MR examinations in the evaluation of the same regions of the body (2000-2002 ￥30.000.000) The Grant-in-Aid for Scientific Research (B)(2) of The Ministry of Education, Science, Sports and Culture in Japan.
2. Abe O.: Cerebral perfusion MR imaging using continuous arterial spin labeling with 2-coil system. (2001-2004 ￥13.600.000)
3. Hayashi N. Optical coherence tomography of the superficial vascular diseases: fundamental study. (2002-2005 ￥13.000.000) Grant-in-Aid for Scientific Research (C) of The Ministry of Education, Science, Sports and Culture in Japan.
4. Nakagawa K. Megavoltage CT-assisted Stereotactic Radiosurgery for Thoracic Tumors (1999-2001, ¥3,500,000)
5. Nakagawa K. Development of computerized questionnaire system for collecting QOL information of cancer patients (2000-2001, ¥3,400,000)

Select Publications (1997-2002, except for 1.27.39) (Department of Radiology)

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7. Aoki S, Hayashi N, Abe O, Shirouzu I, Ishigame K, Okubo T, Nakagawa K, Ohtomo K, Araki T. Radiation-induced arteritis: thickened wall with prominent enhancement on cranial MR images-report of five cases and comparison with 18 cases of moyamoya disease. Radiology 2002 223:683-688
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○10. Hayashi N, Masumoto T, Abe O, Aoki S, Ohtomo K, Tajiri Y. Accuracy of Abnormal Paraspinal Muscle Findings on Contrast-enhanced MR Images as Indirect Signs of Unilateral Cervical Root-Avulsion Injury. Radiology 223(2):397-402,2002.

11. Hayashi N, Tsutsumi Y, Barkovich Polymicrogyria without porencephaly/schizencephaly. MRI analysis of the spectrum and the prevalence of macroscopic findings in the clinical population. Neuroradiology, In print.
12. Yoshikawa T, Aoki S, Hori M, Nambu A, Kumagai H, Araki T. Time-resolved two-dimensional thick-slice magnetic resonance digital subtraction angiography in assessing brain tumors. Eur Radiol 10: 736-744, 2000.
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14.Abe O, Aoki S, Hayashi N, Yamada H, Kunimatsu A, Mori H, Yoshikawa T, Okubo T, Ohtomo K. Normal aging in the central nervous system:quantitative MR diffusion-tensor analysis. Neurobiol Aging. 23:433-441,2002.
○15. Abe O, Okubo T, Hayashi N, Saito N, Iriguchi N, Shirouzu I, Kojima Y,Masumoto T, Ohtomo K, Sasaki Y. Temporal changes of the apparent diffusion coefficients of water and metabolites in rats with hemispheric infarction: experimental study of transhemispheric diaschisis in the contralateral hemisphere at 7 tesla. J Cereb Blood Flow Metab. 20:726-735,2000
16. Mori H, Yoshioka H, Ahmadi T, Saida Y, Ohara K, Itai Y. Early radiation effects on the liver demonstrated on superparamegnetic iron oxide-enhanced T1-weighted MRI.
J Comput Assist Tomogr. 24(4):648-51,2000.
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Contrast-enhanced magnetic resonance imaging of the cranial nerves in patients with acoustic schwannoma: correlation with surgical findings. Acta Otolaryngol Suppl (Norway)542 :13-17,2000
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21. Matsuoka Y, Ohtomo K, Araki T, Kojima K, Yoshikawa W, Fuwa S. MR imaging of clear cell carcinoma of the ovary. Eur Radiol 11: 946-951, 2001
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○27. Nakagawa K, Aoki Y, Akanuma A, Onogi Y, Terahara A, Sakata K, Muta N and Sasaki Y. Real-time beam monitoring in dynamic conformation therapy. International Journal of Radiation Oncology, Biology, Physics 30, 1233-1238, 1994
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○30. Nakagawa K, Aoki Y, Fujimaki T, Tago M, Terahara A, Karasawa K, Sakata K, Sasaki Y, Matsutani M and Akanuma A. High dose conformal radiotherapy influenced pattern of failure, but did not improve survival of glioblastoma multiforme. International Journal of Radiation Oncology, Biology, Physics 40, 1141-1149, 1998
31. Nakagawa K, Aoki Y, Ohtomo K, Albright N and Goer D. Dosimetry of leakage doses from a mobile accelerator for IORT and legal issues for its clinical use in Japan. International Journal of Clinical Oncology 4, 215-219, 1999
○32. Nakagawa K, Aoki Y, Tago M, Terahara A and Ohtomo K. Megavoltage CT-assisted stereotactic radiosurgery for thoracic tumors: original research in the treatment of thoracic neoplasms. International Journal of Radiation Oncology, Biology, Physics 48, 449-457, 2000
33. Tago M, Terahara A, Nakagawa K, Aoki Y, Ohtomo K, Shin M and Kurita H. Immediate neurological deterioration after gamma knife radiosurgery for acoustic neurinoma. J Neurosurg 93, 78-81, 2000
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sies. Japanese Journal of Cancer Research 91, 271-279, 2000
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Nuclear Medicine

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Department of Radiation Oncology (Experimental Radiology)

Outline and Research Objectives

The department was founded in 1966 to carry out education and research on clarification of radiation effect on cells and tissues through biological and biochemical understanding.

Our recent research program(s) have focused on the basic studies for radiation oncology and radiotherapy through understanding molecular biological basis of radiation responses in cells and tissues.

The standardized radiotherapy has been daily fractionated irradiation of 2 Gy for about 6 weeks by which tumor cells lose clonogenic potential while normal tissues involved are saved and recover. To clarify the mechanisms involved in the process and to devise better methods for radiotherapy have been the subject of vigorous study for decades. DNA has been considered as the target for radiation action on the cells causing mitotic or reproductive cell death while a fertilized egg divides into various tissue cells and organs with the same DNA but with different radiosensitivity. Tumors and normal tissues differ in radiosensitivity depending on intrinsic cellular radiosensitivity, cell kinetics, schedule of fractionation, type or quality of radiation used, radiation dose, assay systems used and physiological conditions such as pO_2, pH, nutrient etc. However, the molecular mechanisms for the differences have been little clarified.

Toward this goal the specific projects aimed at the following problems have been planned and in progress.

Specific Aims:

1) To clarify biological mechanisms underlying radiation responses of normal tissues and tumors.
2) To clarify mechanism(s) and signal-transduction pathway(s) of cell death, tissue damage and regeneration after irradiation and/or heat treatment, especially of apoptosis (programmed cell death)
3) To establish predictive assay method(s) such as DNA and protein (antibody) arrays to help select treatment methods, i.e., type of radiation source(s) and irradiating protocol(s) suitable to individual patient and tumor.
4) To develop new methods for sensitization of tumor cells and for prevention of normal tissue damages.

Faculties and Students

Professor and Chair	Norio Suzuki, M.D., Ph.D. (1986~)
Associate Professor	Yoshio Hosoi, M.D., Ph.D.
Associates	2
Graduate students	2
Research students	2

Past Research and Major Accomplishments

1. Quantitative assay system for mutation of cultured mammalian cells
2. Quantification of radiation induced mutation frequencies of mammalian cells in vitro or in vivo
3. Method to determine DNA synthesis point during S-phase using mutation marker
4. Variability and instability of tumor cells in DNA and various malignant properties
5. Clarification of metastatic processes and their relevance to radiation responses in mouse tumor system
6. Cell cycle dependence of metastatic lung colonization in mouse tumor system
7. New assay methods of metastasizing tumor cells released into the blood of mice
8. Characterization of normal tissue stem cells especially testicular spermatogenic stem cells of mouse
9. Existence of hypoxic cells among mouse spermatogenic stem cells
10. Random lifetime and exponential decrease of mouse spermatogenic stem cells

11. Activation of immune response by low dose irradiation
12. Inhibition of metastasis by low dose total body irradiation
13. Sensitization of cells to ionizing radiation by Chlorin e6Na

Current Research

Regarding radiation induced cell death, mitotic or reproductive cell death has been traditionally considered significant and meaningful one underlying tumor cure and tissue damages. DNA double-strand breaks (DSBs) are considered most harmful among various DNA damages induced by ionizing radiation and the primary cause for cell death. Thus, cellular repair capacity of DSBs is a critical factor of radiosensitivity. DSBs are mainly repaired by homologous recombination and non-homologous end joining (NHEJ). DNA-dependent protein kinase (DNA-PK) is required for NHEJ. We have previously reported that inactivation of DNA-PK by wortmannin or other drugs sensitized cells to ionizing radiation.

On the other hand, tumor cells and normal tissue cells have also been known to express apoptotic (interphase) cell death after irradiation and various tumor cells are defective in apoptotic pathway and process. The role and significance of apoptotic cell death in tumor cure or tissue damages depend on histological type or individual tumors and tissues.

We have been focusing currently on clarification of signal transduction and process of cell death, especially apoptotic cell death after irradiation or heat treatment. T cell lymphoma, MOLT-4 cells (p53 wild), and monoblastic U937 cells (p53 null) were mainly used. The other focus has been clarification of the function and the role of DNA-PK in signal transduction of DSB repair and cell death.

1. Signal transduction mechanisms involved in radiation- or heat-induced cell death

As for involvement of receptor-mediated signaling including Fas and TNFR, MOLT-4 cells stimulated by these ligand did not undergo apoptosis, and irradiated cells did not exhibit any mature form of caspase-8, although Fas expression of MOLT-4 was upregulated by irradiation. Dose dependency of p53 expression and dominant negative effect of p53 on radiation-induced cell death of MOLT-4 cells have been reported. Expression of p53-related genes and the mechanism of the mitochondrial pathway are under-investigation.

1-1) Ceramide-JNK pathway

We have recently demonstrated the important roles of ceramide-JNK pathway as well as p53 pathway in radiation-induced cell death of MOLT-4 cells; 1) acid sphingomylinase inhibitor suppressed X-ray-induced apoptosis of MOLT-4 cells. 2) Rh-1a clone, a clone selected for radio-resistance from MOLT-4 cells, was found resistant also to C2-ceramide-induced apoptosis, with less activation of JNK. 3) the activation of JNK after X-irradiation or the treatment with a JNK activator anisomycin caused the decrease of c-Myc expression, 4) the reduction and/or inactivation of c-Myc by c-Myc inhibitor led to apoptotic cell death.

We also demonstrated that the important roles of ceramide-JNK pathway in heat-induced cell death in p53 null U937 cells by the transfection with the dominant negative c DNA of JNK into the cultured cells or the treatment with acid sphingomylinase inhibitor. We are studying further the mechanisms of heat-induced apoptosis and the role of ceramide-JNK signal transduction pathway in the thermo-tolerance development.

1-2) p41-induction in radiation-induced apoptosis

p41, an acidic 41-kDa protein (pI=4.0) was newly found in our laboratory as a radiation-induced protein during apoptotic cell death of irradiated MOLT-4. The protein was detected in two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) and silver staining. The protein appeared radiation dose and time dependent. Amino acid sequence analysis of partial peptides showed homology between p41 and a putative oncogene, *set* (also known as template activating factor I, TAF-I). A polyclonal antibody was raised against a synthetic partial peptide of p41. Immunoblotting analysis of irradiated MOLT-4 cells showed two spots, p41 and an additional 42-kDa protein, p42 (pI=4.1). p42 was detectable also in untreated cells. N-terminal amino acid sequencing of partially purified p41 and p42, and polyclonal antibodies newly raised against different partial peptide sequences revealed that p41 was a N-terminal truncation form of p42, and p42 was identified as SETb (TAF-Ib), one of two SET isoforms. The cleavage site was at carboxyl end of SNHD 18 of p42. A caspase-specific inhibitor or overexpressing of Bcl-2 suppressed radiation-induced p42 cleavage as well as apoptotic cell death of MOLT-4. *In vitro* cleavage experiments with recombinant p42 and either irradiated cell extracts or recombinant caspases, concluded that the cleavage of p42 into p41 was catalyzed by caspase(s) mainly by caspase-7.

One of newly raised antibodies specific to p41 or specific to cleavage site of p42, was found useful enabling simple detection of p41 by 1-D PAGE instead of laborious 2-D PAGE. p41 would serve as a marker of apoptotic cell death. The study on the role and sig-

nificance of p41-induction in radiation-induced apoptosis will be continued.

2. The function and the role of DNA-dependent protein kinase (DNA-PK)

2-1) Target molecules and phosphorylation.

Although more than 30 proteins have been reported as DNA-PK substrates *in vitro*, it has been unknown whether these were true targets *in vivo*. We recently demonstrated XRCC4, a DNA ligase IV-associated protein, as the first example of *in vivo* substrate in response to radiation. We also identified a new phosphorylation site in p53. Through the generation of phosphorylation-specific antibodies and the analysis of phosphorylation-site-disruptants, we are now attempting to clarify the role of the phosphorylation of XRCC4 and p53 in the repair and/or the signal transduction of DNA double-strand breaks.

2-2) Hyperthermic lability and hyperthermic radiosensitization

Radiosensitizing effect of hyperthermia has been widely accepted and applied in cancer therapy. Although many studies proposed various mechanisms for the sensitization, the problem has not been solved and still controversial. We examined hyperthermic stability of purified DNA-PK and its subunits. We found and proposed heat lability of Ku subunit as a possible mechanism for hyperthermic radiosensitization. We also found that the heat stability of DNA-PK was much higher in human cells than in rodent cells, which may reflect the fact that many human cancer cells are more refractory than mouse tumor cells to hyperthermia. We are now studying to modify stability of DNA-PK for improved hyperthermia-radiation therapy.

2-3)Wortmannin affects apoptosis other than repair

Higher concentration of wortmannin such as 5μM or above, which were required for inhibition of DNA-PK and ATM, caused enhanced radiation or heat induced apoptotic cell death in MOLT-4 and V79 cells. The apoptotic process overrode ongoing repair process.

2-4) Prediction of radiation sensitivity.

We found that DNA-PK activity was high in human esophageal and colon cancer tissues compared with control normal tissues. The protein and mRNA expressions of Ku70, Ku80, and DNA-PKcs were also high in the esophageal and colon cancer tissues. The protein and mRNA expressions of Ku70/80 correlated with DNA-PK activity. However, other studies including our own showed various results and the studies are inconclusive.

2-5) Phosphorothioate oligonucleotide and its analogues as inhibitiors of DNA-dependent protein kinase

We are currently studying the functions, the properties and the regulation mechanisms such as post-translational modifications, of key enzymes in DSB repair. We reported that phosphorothioate oligonucleotide and its analogue inhibited DNA-PK activity and sensitized cells to ionizing radiation. The results also showed 1) Correlation between DNA-PK activity and radiation sensitivity 2)) Roles of DNA-PK and ATM in cell-cycle-dependent radiation sensitivity 3) Activation of epidermal growth factor receptor by ionizing radiation

Future Prospects

We hope that these studies will eventually lead us to understanding mechanisms of difference in radiation responses among tissues and tumors, to the discovery and development of radiosensitizers/protectors, and also to the construction of gene/protein array for predictive assay.

Research Grants

1. Scientific Research in Priority Areas (2) (1998-2000, 2001-2002)
   P. I. Norio Suzuki
   "Molecular mechanisms of Radiation-responses and radiosensitivity"
2. Exploratory Research (2002-2003)
   P. I. Norio Suzuki
   "DNA- and Protein-array for radiosensitivity"
3. Scientific Research in Priority Areas (2) (2001)
   P. I. Yoshio Hosoi
   "Prediction of radiation sensitivity and radio-sensitization using DNA-dependent protein kinase"
4. Scientific Research in Priority Areas (2) (2001-2002)
   P. I. Yoshihisa Matsumoto
   "The function of DNA-dependent protein kinase in radiation response and its possible application in cancer radiation therapy I"
5. Grant-in-Aid for Young Scientists (B) (2001-2002)
   P. I. Atsushi Enomoto
   "Analysis of the signal-transduction pathways and the gene expressions using DNA micro-array system on radiation effects"

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Department of System Physiology

Outline and Research Objectives

This department was originally a part of the Research Institute of Medical Electronics operated by the School of Medicine, but in 1997, when the University of Tokyo restructured its system of education and research, the Institute became the Division of Biomedical Engineering in the Graduate School of Medicine. The Division of Biomedical Engineering consists of three departments: Bioimaging and Biomagnetics, Biosystem Construction and Control, and our own System Physiology.

This laboratory has been pursuing research on the biomechanics of phenomena in the human body, especially focusing on cellular sensing and response mechanisms to mechanical stimuli. The main theme of our work has been the relationships between the mechanical force generated by blood flow, shear stress and the cells exposed to it, vascular endothelial cells. Research on this theme will be of benefit not only in understanding blood-flow-mediated regulation of vascular functions but in elucidating issues that are of importance clinically, such as angiogenesis, vascular remodeling, and atherogenesis, all of which occur in a blood flow-dependent manner.

Original biomedical engineering methods have been applied in which cultured endothelial cells are exposed to controlled levels of fluid shear stress in a dynamically designed flow apparatus (Fig. 1) and their responses are analyzed at the cellular and molecular levels.

Faculty and Students

Professor and Chair	Joji Ando, M.D., Ph.D. (since 2000)
Lecturers	Masahiro Shibata, Ph.D.
Associates	1
Graduate Students	3

Past Research and Major Accomplishments

Our studies have involved experiments on the following:

1. Endothelial cell responses to shear stress
2. Shear stress-mediated regulation of endothelial gene expression
3. Shear stress signal transduction in endothelial cells
4. In vivo analysis of blood flow effects

And the results are described below.

Endothelial cell responses to shear stress

Our studies have demonstrated that endothelial cells exhibit functional responses to shear stress. When a cultured endothelial cell monolayer was partially denuded, surrounding cells migrated and proliferated in the denuded area, and covered it. Shear stress enhanced the regenerative functions of endothelial cells (Microvasc Res 1987, Biorheology, 1990), and it increased the production of nitric oxide, a potent vasodilator, in endothelial cells in a dose-dependent manner (BBRC 1994). It also increased the expression of thrombomodulin, an antithrombotic molecule, in endothelial cells (BBRC 1994). By contrast, shear stress decreased the expression of vascular cell adhesion molecule-1(VCAM-1), which led to inhibition of leukocyte adhesion to endothelial cells (BBRC 1993, Am J Physiol 1994). A collaborative study

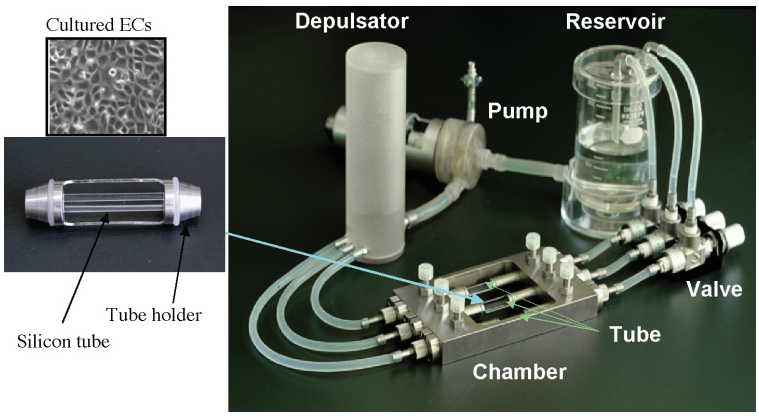

Fig. 1. A silicon-tube-type flow-loading apparatus.

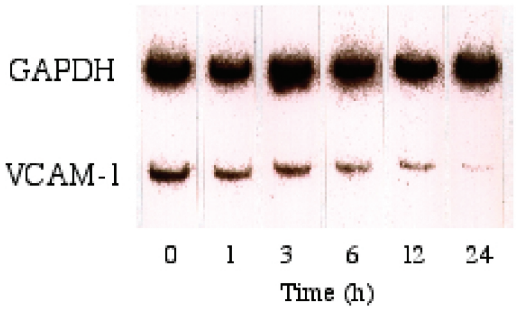

Fig. 2. Downregularion of VCAM-1 mRNA levels by shear stress.

showed that shear stress increases the levels of adrenomedulin and C-type natriuretic peptide mRNA, which have vasodilating effects (Hypertension 1997), and that it augments the expression of low density lipoprotein receptor (LOX-1) at both the protein and mRNA level (Circ Res 1998).

Shear-stress-mediated regulation of endothelial gene expression

We have demonstrated that shear stress regulates endothelial gene expression transcriptionally and/or posttranscriptionally. It downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGACTCA) in the promoter, which functions as a shear stress-responsive element (Am J Physiol 1997).

Fig.2 shows shear stress-induced changes in VCAM-1 mRNA levels determined by the reverse transcriptase PCR method. Shear stress has also been shown to increase the level of granulocyte/macrophage-colony stimulating factor (GM-CSF) via mRNA stabilization (Circ Res 1988). Differential display analysis showed that approximately 600 known and unknown transcripts are up- or down-regulated in human umbilical vein endothelial cells exposed to a shear stress of 15 dynes/cm^2 for 6 h (BBRC 1996), and a cDNA encoding an unknown G-protein coupled receptor was cloned from these shear stress-responsive genes (BBRC 1997).

Shear-stress signal transduction in endothelial cells

We were the first to show that Ca^{2+} signaling plays an important role in the mechanism by which endothelial cells recognize the shear stress signal and transmit it into the cell interior (In Vitro Cell Dev Biol 1988) . Strong shearing forces induced by rubbing endothelial cells with a balloon cause an increase in cytoplasmic Ca^{2+} concentrations (Biorheology 1994). A relatively weak shearing force, such as the shear stress generated by fluid flow, requires the presence of extracellular ATP to induce a Ca^{2+} response, and at several hundred nanomolar ATP, intracellular Ca^{2+} concentrations increase in a shear-stress-dependent manner (BBRC 1991, 1993). Flow-induced Ca^{2+} responses generally start at a locus at the cell edge and propagate throughout the entire cell in the form of a Ca^{2+} wave (Fig. 3). The initiation locus corresponds precisely to caveola-rich cell edges (Proc Natl Acad Sci 1998). We recently found that a subtype of ATP-gated cation channel, the P2X4 receptor, is expressed in human vascular endothelial cells and that P2X4 receptors play a crucial role in the shear stress-dependent Ca^{2+} response (Am J Physiol 2000, Circ Res 2000).

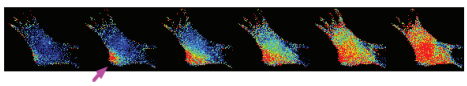

Fig. 3. A flow-induced Ca^{2+} wave in an endothelial cell.

In vivo analysis of blood flow effects

Blood flow effects on capillary permeability to macromolecules and angiogenesis have been investigated in vivo by intravital microscopy. We developed a new intravital slit-laser microscanning method to quantitatively measure permeability to fluoresecent-labeled proteins at the distal end of arterioles, the middle of capillaries and the proximal end of venules in rabbit skeletal muscle tissue (Microvasc Res 1995, 1997). Permeability has been shown to increase with blood flow, indicating that shear stress regulates capillary protein permeability (Jpn J Physiol 1991, 1992). We also investigated the relationship between capillary blood flow and tissue oxygen demand (Microvasc Res 1985). We observed that increases in blood flow, which were induced by arterio-venous shunt or administration of a-blocker, augmented the formation and development of new capillaries (Microvasc Res 1998). Our computer simulations have demonstrated that formation of capillary networks in mammals corresponds well to an optimum model calculated from the oxygen supply efficiency in tissues (Microvasc Res 1995). An intravital laser microscope that utilizes a phosphorescence quenching technique was recently developed to determine both microvascular and interstitial oxygen concentrations (J Appl Physiol 2001).

Current Research

Ongoing research in our laboratory include projects designed to 1) identify molecules that function as a flow sensor or shear-stress sensor in endothelial cells, 2) analyze endothelial genes that respond to shear stress, 3) investigate effects of shear force on the differentiation of endothelial progenitor cells, 4) study the microcirculation.

Flow-sensing molecules: Our recent studies have revealed that endothelial cells convert information on shear stress into changes in intracellular Ca^{2+} concen-

trations, and that P2X4 purinoceptors and their ligand ATP play an important role in the Ca^{2+} signaling. To examine the role of P2X4 receptors as flow-sensors, P2X4 cDNA was transfected into human embryonic kidney (HEK) cells, and cell lines that stably express P2X4 receptors were established. As shown in Fig. 4, the control HEK cells did not show any Ca^{2+} response to shear stress, whereas HEK cells that stably expressed P2X4 receptors showed a shear stress-dependent Ca^{2+} response. Thus, ectopic expression of P2X4 receptors made the HEK cells sensitive to flow, suggesting that P2X4 receptors function as a flow sensor. More recently, it has been demonstrated that endothelial cells release ATP in response to shear stress, and the endogenously released ATP is involved in the activation of P2X4 receptors. Shear stress-sensing mechanisms are currently being investigated in terms of ATP release.

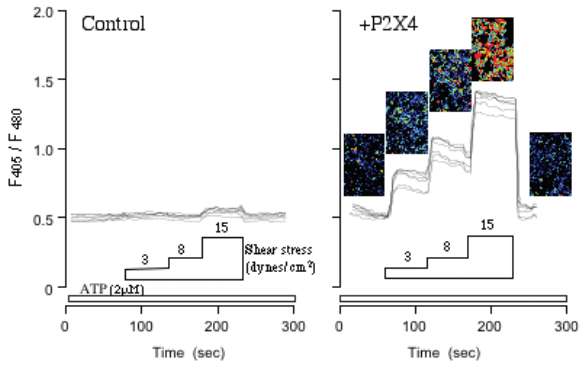

Fig. 4. P2X4 cDNA transfection makes HEK cells sensitive to shear stress.

Shear-stress-responsive genes: A high throughput genomic analysis of gene expression using DNA microarrays has been used to gain a more complete appreciation of the extent and biologic significance of endothelial activation by shear stress. Comparison of the transcriptional activity of approximately 6,000 unique genes has revealed that laminar shear stress up- or down -regulates the expression of approximately 4% of the genes examined in endothelial cells. Turbulent shear stress, which is closely related to the conditions under which atherosclerosis develops, changed the expression of about 1.5% of the genes examined. These genes included many of the genes known to function in vascular remodeling, such as genes encoding plasminogen activator, transforming growth factor and metalloproteinase. Attention is now focused on the role of these shear stress responsive genes in atherogenesis.

Effects of shear force on cell differentiation: Endothelial progenitor cells (EPCs) have recently been found to circulate in blood vessels, migrate into tissues, and participate in neovascularization, and we recently observed that shear stress augments proliferation, differentiation, and tube-formation by EPCs. This means that mechanical forces can manipulate the differentiation of EPCs. These techniques are of potential use in clinical applications, such as in the development of tissue-engineered vessels and cell therapy for ischemic vascular diseases.

Microcirculation study: Oxygen-sensing molecules that play an important role in the regulation of vascular resistance are now being investigated, and an in vivo optical method has been developed to monitor pO2 distribution in skeletal muscle arterioles. We have observed a significant drop in pO2 in the arterioles and a large pO2 gradient in the arteriolar walls, indicating that the endothelial cells and/or smooth muscle cells of arterioles may consume much more oxygen than expected. We are also developing an in situ vascular Ca^{2+}imaging system to explore the cellular mechanism of the effects of flow and hypoxia on vascular tone.

Future Prospects

We intend to expand our research vascular biomechanics research to research on tissue engineering, atherosclerosis, and the vascular physiome in the near future.

Vascular biomechanics: To elucidate the physiological or pathophysiological significance of shear stress, shear stress-sensing molecules will be identified and knockout mice will be produced. Novel drugs that can modulate the shear stress sensors will be developed and applied to the treatment of vascular diseases.

Tissue engineering: Techniques for manipulating cell functions by mechanical forces will be developed and applied to the preparation of tissue-engineered blood vessels. A technique that allows reconstitution of endothelial progenitor cells to a 3-dimensional, capillary-like structure under flow conditions will be used to produce engineered capillary network tissue. The capillary module will be expanded to an innovative tissue engineering approach to produce blood-vessel-containing engineered tissues, such as liver and myocardial tissue.

Atherosclerosis research: Athero-prone or -protective genes will be identified among genes that respond to turbulent shear stress. An in vitro model of tissue-engineered atheroma will be established by arranging conditions, such as genetic background, hemodynamics, and lipids related to atheroscelerosis. The results of these studies may be useful in develop-

ing a novel therapy for atherosclerosis.

Vascular physiome: The term "physiome" is derived from "physio- (life)" and "-ome" (as a whole), and means the quantitative and integrated description of physiological functions based on information on the genome, and proteome, and bioinformatics. Mechanical forces generated in blood vessels regulate vascular growth and remodeling in the human body. An integrative description, including modeling, of the mechanical force-mediated vascular controlling system will be conducted, and this is called the "vascular physiome".

Research Grants

1. Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology
   Basic Research (A) 1995-1996 23,000, 000 Yen
2. Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology
   Basic Research (A) 1997-1998 21,500, 000 Yen
3. Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology
   Basic Research (A) 1999-2000 27, 900, 000 Yen
4. Special Coordination Funds for Promoting Science and Technology from the Japanese Ministry of Education, Culture, Sports, Science and Technology
   1998-2002 28, 000, 000 Yen
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Department of Bioimaging and Biomagnetics

Outline and Research Objectives

Our department was established in 1974, with the objective of promoting research on engineering science in medicine and biology. In April, 1994, Professor Shoogo Ueno joined the University of Tokyo, replacing retiring Professor Masao Saito as chairman of the Division of Engineering Science in the Institute of Medical Electronics. In April 1997, our division re-established itself as the Department of Bioimaging and Biomagnetics. Since its establishment in 1994, the Department of Bioimaging and Biomagnetics has been engaged in research on engineering science in medicine and biology. Our department specializes in biomagnetic research, which includes the measurement of biomagnetic fields, magnetic stimulation of the brain, and the effects of magnetic fields on biological systems.

Faculties and Students

Professor and Chair	Shoogo Ueno, Dr. Eng. (1994~)
Associate Professor	Keiji Iramina, Dr. Eng.
Lecturer	Masakazu Iwasaka, Dr. Eng.
Postdoctoral Fellow	: 1
Graduate Student	: 15
Research Student	: 1
Secretary	: 2

Past Research and Major Accomplishments

We have studied the measurement and control of biological systems based on biomagnetism. We develop, integrate, and apply new ideas through innovative interdisciplinary research approaches. Our research topics cover wide areas in medical and biological engineering, including technology for measurement, imaging, and modelling in the following fields.

Magnetic stimulation of biological systems

Measurement of biomagnetic fields

Imaging of Electrical Information Based on Magnetic Resonance Imaging (MRI)

Effects of magnetic and electromagnetic fields on biological systems and materials

(1) Transcranial magnetic stimulation (TMS) has become an important tool for the study of the functional organization of the human brain. We developed a method of localized and vectorial magnetic stimulation using a figure eight coil (Fig.1). This method facilitates stimulation of the motor cortex of the human brain within a 5 mm resolution. We studied the cortical excitatory and inhibitory systems, using the technique of paired TMS. We observed that TMS initiates the excitation of both cortical interneurons and pyramidal tract neurons. Once the pyramidal tract neurons generate a D-wave, the excitation is unaffected by a conditioning stimulus, which has an inhibitory effect on excitability of pyramidal tract neurons.

(2) For the measurement of biomagnetic fields, we developed a SQUID (superconducting quantum interference device) system with high sensitivity that facilitates the measurement of auditory brainstem evoked magnetic fields.

We studied higher brain functions associated with short-term memory and mental rotation processes using MEG. In the functional information related to short-term memory processes, a DC-like slow wave was observed in the period between latencies of 900

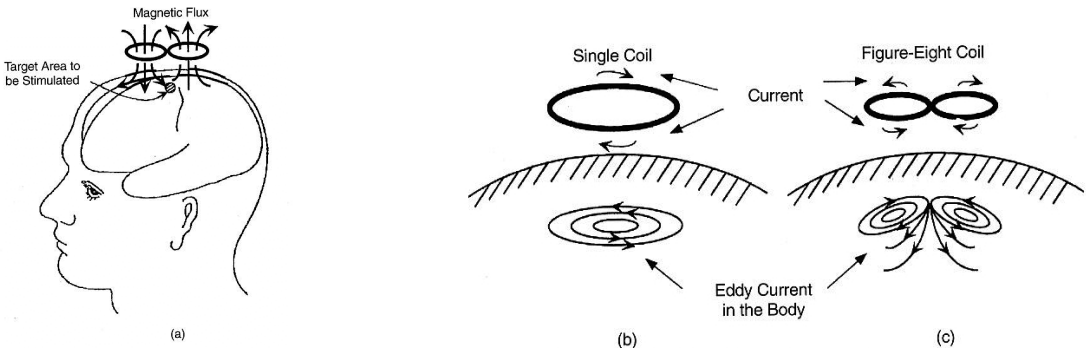


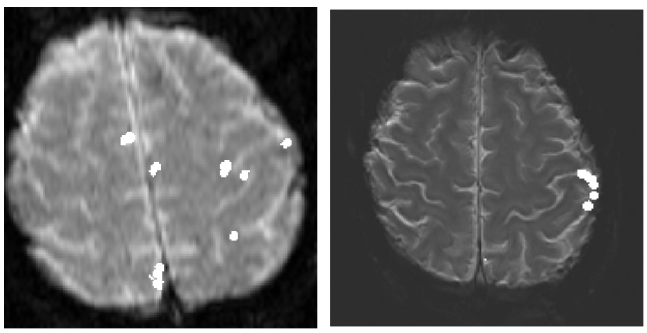
Fig.1 Basic principles of magnetic stimulation using a figure-eight coil. (a) A figure-eight coil on the head. (b) A single ring coil and an induced current pattern. (c) A figure-eight coil and an induced-current pattern.

msec and 1,500 msec during the short-term memory task. A mental rotation process requires rotation and matching of a pair of mental images. Dynamic properties of the electrical current distribution in the human brain that correspond to the early mental rotation processes were investigated.

We also focused on the relationship between MEG and fMRI and we studied the temporal and spatial responses of both hemodynamic and neuronal activities. Activation of the primary somatosensory cortex was investigated using MEG and fMRI. It was possible with fMRI to discriminate between the area of the thumb and the ring finger in the primary somatosensory cortex. In MEG measurement, however, it is difficult to discriminate between two closely located dipoles, if no initial information is given.

(3) Conventional MRI does not reveal information about the electrical properties of the body. We developed new methods to visualize neuronal current distribution and electrical-impedance distribution. The basic principle is to erase the effects of BOLD (blood oxygenation level dependent) by subtracting MRI signals with different polarities of gradient magnetic fields. Measurements were made with an echo planar imaging (EPI) sequence at 1.5 T. MRI mapping of the neuronal currents in the brain during middle finger and thumb tapping was clearly observed (Fig.2). A new method for impedance tomography was introduced, based on MRI techniques. The basic idea of impedance imaging is to use the shielding effects of induced eddy currents on spin precession.

(4) We investigated the dynamic behavior of water in high gradient magnetic fields. A superconducting magnet that produced 8 T magnetic fields at the center was used. The maximum product of the magnetic field and the gradient was 400 T^2 / m at z = 75 mm, where the z-axis was directed along the bore axis. A water chamber, 50 mm wide, 60 mm high, and 700 mm long was filled with distilled water. When the water chamber was inserted into the bore, we observed the phenomenon in which the water was parted, and the bottom of the water chamber was revealed. We call this phenomenon the Moses Effect. A simple calculation shows that the magnetic force acting on 100 ml of water at 20 ℃ is 0.288 N or about 1/3 of the earth's gravity, when exposed to a magnetic field of 8 T and 50 T/m. Since the magnetic force acting on diamagnetic and paramagnetic materials moves the materials along magnetic field gradients, any kind of biological cells and materials can be manipulated by magnetic force. In contrast, when biological materials such as fibrin and collagen are exposed to uniform magnetic fields, parallel or perpendicular orientation to the magnetic field direction is attained. For example, we successfully oriented adherent cells such as smooth muscle and endothelial cells, and osteoblasts in parallel to the magnetic field direction after 8T magnetic field exposure (Fig. 3). The magnetic manipulation and alignment of cells and other biological materials has opened a new horizon in tissue engineering.



(a) fMRI (b) current MRI

Fig.2 (a) fMRI and (b)MRI mapping of the neuronal currents in the brain during middle finger and thumb tapping.

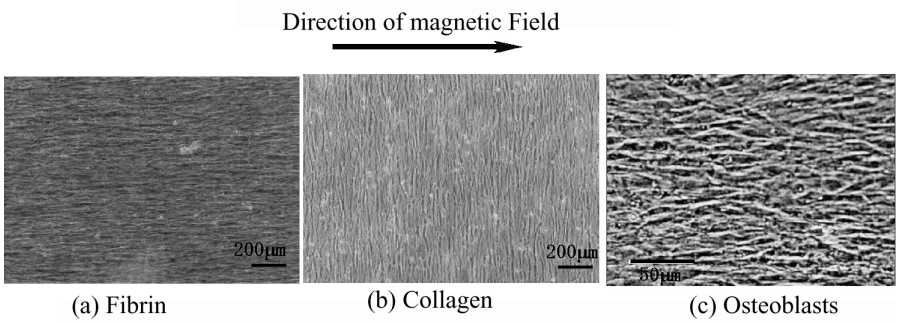


Fig.3 Magnetically oriented (a) Fibrin (b) Collagen (c) Osteoblasts under an 8T static magnetic field.

Current Research

Our department is conducting interdisciplinary research in three major areas: imaging and cognitive neuroscience, cell and tissue engineering, and the assessment of the biological effects of electromagnetic fields.

Imaging and cognitive neuroscience

Our research focuses on the development of functional brain dynamics imaging with high time resolution and high spatial resolution. The main techniques employed are TMS (transcranial magnetic stimulation), MEG (magnetoencephalography), EEG (electroencephalography), electric current imaging by MRI, and impedance imaging by MRI. These techniques are noninvasive and very useful for studying higher brain functions of humans such as memory and cognition.

We developed a 2-channel repetitive transcranial magnetic stimulator and an EEG measurement system that combines TMS. We were able to non-invasively evaluate the cortical reactivity and functional connections between different brain areas. We used TMS to investigate memory encoding and retrieval, particularly the role of the dorsolateral prefrontal cortex in associative memory for visual patterns. TMS disrupts associative learning for abstract patterns over the right frontal area, which suggests that the participating cortical networks may be lateralized in accordance with classic concepts of hemispheric specialization.

We compared current density distributions in electroconvulsive therapy (ECT) and TMS using the finite element method. While the skull significantly affected current distributions in ECT, TMS efficiently induced eddy currents in the brain. Our results will support clinical investigations to determine the electrode and coil positions that maximize efficacy.

To investigate the safety aspects of TMS on the brain, functional and anatomical changes in the brain were investigated. Our initial experimental results revealed that TMS does not affect the fEPSP (field excitatory post synaptic potential) of the rat hippocampus.

We introduced a new method of conductivity tensor imaging using diffusion-weighted MRI to obtain conductivity tensor distribution of the brain. Diffusion-weighted images were acquired with motion probing gradients (MPGs) applied in three directions. Conductivities in each MPG direction were calculated from the fast component and the fraction of the fast component, and two-dimensional conductivity tensor was estimated. We also proposed a new method of electrical current imaging based on the frequency shift technique of MRI.

In another study, we investigated a method for tissue characterization using diffusion tensor analysis and applied external electrical currents.

Magnetophysiology

We studied the ischemic myocardial muscles of rat using a high-resolution DC-SQUID magnetometer. The information about the ischemic myocardium region and changes of function were obtained by caridiomagnetic imaging.

We also measured the magnetic fields associated with end plate potentials induced from neuromuscular junctions of frogs. Biomagnetic measurements of synaptic transmission processes by micro SQUID systems are useful for the physiological and pharmacological studies such as stimulus-excitation-contraction coupling.

Biological effects of electromagnetic fields

We investigated the effects of strong magnetic fields (8T, 14T) on the structure, organization, and function of biological systems and materials, and the possible medical and therapeutic applications of magnetic fields.

The effects of 14 T strong static magnetic fields on the functional properties of biological materials, such as proteins, oxygen molecules, and water were also investigated. (1) A spectrum profile of hemoglobin inside red blood cells indicated conformational changes depending on the magnetic flux density. (2) Magnetic field exposure initiated platelet aggregation with the aid of collagen and accelerated the aggregation of platelets and fibrin. (3) Leukemia cell proliferation was decreased by an 8 T magnetic field, as a result of behavioural changes of dissolved oxygen during exposure. (4) Magnetic fields inhibited bioluminescence of luciferin and luciferease in both in vitro and in vivo experiments. Possible applications of magnetic fields for the control of biochemical reactions were suggested.

We explored the possible medical applications of magnetically oriented collagen. Magnetically aligned collagen provides a scaffold for smooth muscle cells (A7r5), osteoblasts (MC3T3), nerve cells (PC12 and Schwann cells), and blood vessels on which to grow, and it directs the growth to a specific direction. Further experiments, however, demonstrated the magnetic orientation of adherent cells without collagen guidance after long-term exposure to static magnetic fields. Further studies must be carried out to clarify the detailed mechanisms which include the diamagnetic properties of the cells. Our findings may lead to clinically viable treatments of bone fractures and bone defects as well as medical engineering applications such as nerve regeneration.

With the ever-increasing worldwide use of mobile phones in recent years, social concerns and anxieties have been raised about the possible detrimental

effects on human health. We investigated the effects of high frequency electromagnetic field exposure on rats.

We investigated the effects of exposure to the standard frequency of electromagnetic waves used for cellular phones in Japan (1,439 MHz) on the permeability of the blood brain barrier (BBB), brain morphological changes, body mass fluctuations, and cognitive functions and memory restoration of male Sprague-Dawley rats.

Our results suggest that exposure to a TDMA field at levels much stronger than emitted by cellular phones do not affect the learning and memory processes when there are no thermal effects. In our most recent study, however, we investigated the effects of 1439 MHz TDMA electromagnetic fields on sleep disturbance or melatonin synthesis in rats. The pineal melatonin level decreased with short-term TDMA exposure, whereas the serum melatonin level was unchanged. Short-term TDMA exposure may inhibit pineal melatonin synthesis in this limited experiment. Further studies are currently underway to confirm and explain our initial results.

Future Prospects

In the next 3.5 years, we hope to achieve significant progress in our three major areas of research: imaging and cognitive neuroscience, cell and tissue engineering, and the assessment of biological effects of electromagnetic fields.

By determining how the brain works, from the level of neurons to the relationships between complex neural networks, a myriad of medical, therapeutic and engineering applications will be developed. The combination of neuromagnetic imaging techniques will allow us to understand the dynamic interactions between individual cells and larger neural networks that give rise to the patterns of electrical activity associated with higher brain function. We hope to determine where and how signals for various higher cognitive processes arise within the brain using TMS, EEG, MEG, and MRI. The development of new imaging methods to better visualize brain activity will also provide a wealth of new information. For example, our new MR imaging techniques will be helpful for the early detection of neurological disorders, such as acute cerebral infarctions. Ultimately, we hope the information retrieved will uncover the roots of neurological and psychiatric diseases.

By determining the effects of electromagnetic fields on biological materials and systems and understanding the mechanisms involved, we can develop many potentially viable cell and tissue engineering applications. For example, we will continue our research to determine whether repetitive TMS regenerates or prevents damage to injured rat hippocampal CA3 cells as well as our study on the magnetic orientation of Schwann cells for nerve regeneration. Researches on the cellular responses to magnetic fields will also proceed by analyzing the genetic responses as well as the morphological changes of cells under strong static magnetic fields. Magnetically induced cytoskeleton displacement in an intact cell will be observed during both long and short-term magnetic field exposures. A new technique for the remote handling of macromolecules in living systems by electromagnetic forces will also be developed.

Research Grants

1. 2000-2004 Grant-in Aid for Specially Promoted Research, Ministry of Education, Science, Sports, Culture and Technology, Japan (No. 12002002.) 386,000,000Yen "Study of Dynamic Brain Function using Transcranial Magnetic Stimulation and Neuronal Current Imaging"
2. 1998-2000 Grant-in Aid for Scientific Research (A), Ministry of Education, Science, Sports, Culture and Technology, Japan (No. 10308037) 35,800,000Yen "Control of living systems by strong magnetic fields"

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Department of Biosystem Construction & Control

Outline and Research Objective

This department was established in 1964 as Division of Clinical Medicine in Institute of Medical Electronics for research and development of the advanced diagnostic and therapeutic instruments for the clinical medicine and their related technologies. The education to train the leaders of biomedical engineer and clinical engineer is its another important role. The first The name of the department and institute has been changed as shown above since April 1, 1997 with the structural reform of Faculty of Medicine.

This department has been cooperating with Division of Artificial Biomechanism, Research Center for Advanced Science and Technology (RCAST) presided by Associate Prof. Chinzei and Division of advanced Biomedical Engineering & Life Science, Center for Cooperative Research (CCR) presided by Prof. Mabuchi in the recent 10 years. Both laboratories, 10 Km distant, are connected with a personal microwave television system for all-day long to exchange many information, to have a periodical research meeting and to monitor the artificial heart animals from each other.

Our research fields are artificial heart, artificial valve, biomaterials, medical laser, medical thermography, measurement instruments and sensors, and micromachine.

Faculties and Students

Professor and Chair	Kou Imachi, Ph. D.(1993 -)
Associate Professors	Yusuke Abe, M. D., Ph. D.
Lecturer	Takashi Isoyama, Ph. D.
Associate	1
Technical Assistant	1
Graduate Students	2
Guest Researchers	6
Secretary	1
Professor Emeritus	Kazuhiko Atsumi, M. D., Ph. D., Iwao Fujimasa, M. D., Ph. D.

Past Research and Major Accomplishments

Professor Imachi joined to Institute of Medical Electronics in 1970 as a student of Graduate School of Medicine, University of Tokyo, after he got the master's degree of mechanical engineering at Kyoto University and spent 2 years at Hitachi Chemical Co. Ltd. as a chemical plant research engineer. Since that time he has been studying biomedical engineering and he became Associate in 1972, Associate professor in 1987 and Professor in 1993. The past research and major accomplishments performed by him and his group are shown in the following;

1. Artificial heart

The artificial heart(AH) study is world famous research project having a long history since 1959. Almost all the research fields such as driving mechanism, blood pump, artificial valve, materials, measurement & control method, circulatory physiology and pathophysiology have been developed and studied. They are summarized in Figure1.

Our peculiar policy for AH research is shown in Table 1. According to the policy, we have been approaching to an implantable total AH(TAH) with quite different way from other groups and have obtained many accomplishments summarized in Table 2. Among these accomplishments, trying 4 types of TAH, development of jellyfish valve, device of 1 / R control method, 3 times of the world longest survival record under TAH goat, proposal of many pathophysiological hypothesis, and invention of undulation pump are the most unique and remarkable outputs.

2. Biomaterials

Concerning the biomaterials, the mechanism of thrombus formation and calcification on the medical polymer surfaces, especially in the artificial heart blood pump and on polymer valve have been studied. The evaluation of biocompatibility of many biomaterials was also important task.

3. Medical laser

Medical laser research in this laboratory was started in 1965. Ruby laser, CO_2 laser, Nd-YAG laser, excimer laser, argon laser, semiconductor laser have been studied. Laser scalpel, laser coagulator, laser endoscopes for percutaneous intradiscal laser nucleotomy, for colonary laser angioplasty and for percutaneous mitral valvotomy, were developed. As

Fig. 1 History of TAH in The University of Tokyo

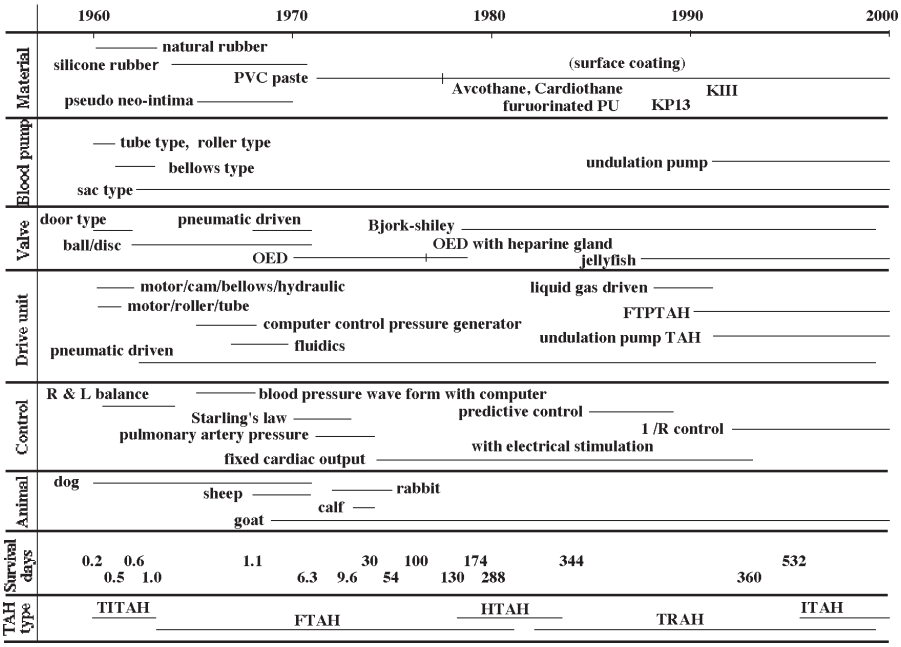

Table 1 The policy of AH research in our laboratory

Never copy the foreign countries project (respect the other person's originality)
Don't be captured by the existing laws and theories
(there is no common sense in interdisciplinary field research)
Don't cling to your background
Have always hypothesis
Don't change the system until it runs into a stone wall
Don't change more than 2 parameters at once
Try to make all the things by yourself (Speed is the most important)
Don't hesitate to publish the negative data (truth is hidden in the negative data)

Table2 Accomplishments in AH research in this laboratory

Four types of TAH,: FTAH(1963-1980), HTAH(1977-1982), TRAH(1981-1996) and ITAH(1996-)
- FTAH: TAH with fibrillated natural heart
- HTAH: Hybrid TAH, Natural heart is beating but trunks of PA and Ao is occluded
- TRAH: Total replacement AH, NH is resected and 2 pumps are placed on the chest wall
- ITAH: Implantable TAH, All the components except energy source are implanted

Home made artificial valves
- OED(Oblique elliptical seat door type) valve 1971 - 1978
- Jellyfish valve: polymer membrane valve(1987 -)

Control method
- Fixed cardiac output
- Fixed cardiac output with electrical stimulation
- 1 / R control

World longest survival record with TAH in goat
- 1980: 288 days with HTAH
- 1984: 344 days with TRAH
- 1995: 532 days with TRAH under 1 / R control

Hypothesis
- Hyper cardiac output syndrome: 1973 - 1975
- Cardiac receptor hypothesis:: 1982 - 1895
- Calcification mechanism hypothesis: 1995 - 2000

Blood pump & materials
- Critical surface roughness to promote thrombus for mation(3 mm): 1970
- Surface coating of segmented polyurethane on PVC: 1973 -
- Multi-material test method of blood compatibility: 1984 - 1990

Clinical device development
- Pneumatic driven ventricular assist device in cooperation with Aisin Seiki & Nippon Zeon Co. Ltd.:1990 -

for the basic research, the influence of various kinds of lasers on living tissue, laser therapy for tumor and cancer, laser neurotomy, bactericidal effect of laser were investigated.

4. Medical thermography

Research of medical thermography in this laboratory was started in 1965. Since that time, many kinds of infrared thermography for clinical use has been developed in cooperation with Fujitsu, Nihon-denshi, NEC, Nihonkoden Co.Ltd, etc.. As the basic and application researches, theoretical model construction to estimate subcutaneous blood flow from thermogram, digital processing of thermogram, dynamic thermography, standardization of clinical daignosis, thermotome, thermo-myotome, etc were studied.

5. Measurement instruments and sensors

Portable electro-magnetic flow(EMF) meter, EMF flow probe for AH, blood lactate measurement instrument, remote monitoring system of AH animals through microwave TV, implantable CCD probe to observe microcirculation were developed.

6. Micromachine

Micromachine research was started in 1987. The word "micromachine" was made in this laboratory when we began to start a society for the study of micro-mechanical system in 1988. Artificial muscle moved by vibrating energy, regenerative nerve electrode, micro-laser endoscope were studied and developed

Current Research

1. Artificial heart

Since 1996, AH project in this laboratory is focused on the development of implantable TAH in which the all components except outer battery and energy transmission system are implanted into the body and expected as the substitution of the heart transplantation. Undulation pump TAH(UPTAH) which is the most compact TAH in the world was invented(Fig. 2). Another merit of UPTAH is that it can produce any kinds of flow patterns such as pusatile flow, continuous flow and pulsatile flow on the continuous flow, etc.. At the present stage, 6 goats survived over 1 month including 63 days as the longest. Now all the components such as blood pump, driving unit, control system, measurement system and energy transmission system are being made more compact and increased in durability and reliability. The influences of nonpulsatile flow on microcirculation and organ function are being in research. A new

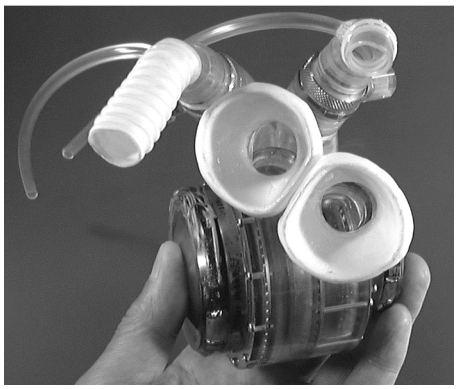

Fig.2 Assembled UPTAH

project to develop an implantable ventricular assist device for clinical use for the bridge to heart transplantation has been ready to start using the undulation pump. According to our calcifiction hypothesis, the jellyfish valve is improved design to reduce the creep fatigue. The new designed valve proved almost 10 years durability in-vitro acceleration fatigue testor.

2. Other researches

In the laser research, handy type laser blood coagulator aiming to use in the surgical field, is being developed and evaluated in the animal experiments. The imaging of arterial blood flow distribution in the skin and organs using a high speed thermography is studying. CCD probe to observe microcirculation chronically is being made compact including focus. Regenerative nerve electrode to control artificial organs through nervous signals is improving its tissue compatibility.

3. New research

Tissue engineering research has started in this year. As the first step, valve membrane of jellyfish valve is trying to make using endothelial cell culture.

Future Prospects

The following researches are scheduled as the future projects and a part of them is already ready to start.

Development of a permanent use artificial heart to be able to substitute the heart transplantation. A rotary type undulation pump which moves magnetically suspended is begun to design.

Complete the regenerative nerve electrode and find a control algorithm of artificial organs through nervous signals.

Development distributed artificial heart system in which the artificial blood pumps are connected to each organs and tissues. Basic study to connect a small AH to a kidney has already started.

Regenerative medicine to make a whole organs from ES cells will be started aiming to how to shortening the growing time utilizing a biomedical engineering technologies.

Research Grants in these 5 Years

1. The Program for Promotion of Fundamental Studies in Health Science of the Organization for Pharmaceutical Safety and Research(OPSR) " The comprehensive basic research on the development of Japanese original implantable total artificial heart", Head Investigator: K. Imachi, 170,460,000yen, 1996 – 2000
2. Grant-in-Aid for Scientific Research (B)(2):" A study on long-term and continuous observation and analysis of microcirculation under artificial circulation", Top Head Investigator: K. Imachi, 16,000,000yen, 1999 – 2000
3. Grant-in-Aid for Scientific Research (A)(2): " Development of a simplified pulsatile left ventricular assist device", Head Investigator: K. Imachi, 17,200,000yen, 1999 – 2000
4. Grant-in-Aid for Scientific Research (A)(2):"Research and development of implantable artificial heart for permanent use", Head Investigator: Y. Abe, 42,600,000yen, 2000 – 2002
5. Grant-in-Aid for Scientific Research (S): "Comprehensive research for the influence of flow state of artificial heart on the living body by observation of microcirculation", Head Investigator: K. Imachi, 87,900,000yen, 2002 – 2006

Select Publications

1. K. Atsumi, Y. Sakurai, I. Fujimasa, K. Imachi, T. Nishisaka, I. Mano, H. Ohmichi, J. Mori, N. Iwai and A. Kouno: Hemodynamic analysis on prolonged survival cases (30 days and 20 days) of artificial total heart replacement, Trans. Am. Soc. Artif. Intern. Organs, 21,545-554, 1975.
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