

Fig. 2: Schematic drawing of the quasi-monochromatic x-ray tube.

## 2. Generator

Figure 1 shows a block diagram of a compact characteristic (quasi-monochromatic) x-ray generator. This generator consists of the following components: a constant high-voltage power supply (SL150, Spellman Inc.), a DC filament power supply, a turbomolecular pump, and an x-ray tube. The structure of the x-ray tube is illustrated in Fig. 2. The x-ray tube is a demountable diode which is connected to the turbomolecular pump with a pressure of approximately 0.5 mPa and consists of the following major devices: a molybdenum plate target, a tungsten hairpin cathode (filament), a focusing electrode, a polyethylene terephthalate x-ray window 0.25 mm in thickness, and a stainless-steel tube body. In the x-ray tube, the positive high voltage is applied to the anode (target) electrode, and the cathode is connected to the tube body (ground potential). In this experiment, the tube voltage applied was from 22 to 36 kV, and the tube current was regulated to within  $100 \mu\text{A}$  by the filament temperature. The exposure time is controlled in order to obtain optimum x-ray intensity. The electron beams from the cathode are converged to the target by the focusing electrode, and x-rays are produced through the focusing electrode. Because bremsstrahlung rays are not emitted in the opposite direction to that of electron trajectory, clean molybdenum K-series x-rays can be produced without using a filter.

## 3. Characteristics

### 3.1 X-ray intensity

X-ray intensity was measured by a Victoreen 660 ionization chamber at 1.0 m from the x-ray source (Fig. 3). At a constant tube current of  $100 \mu\text{A}$ , the x-ray intensity increased when the tube voltage was

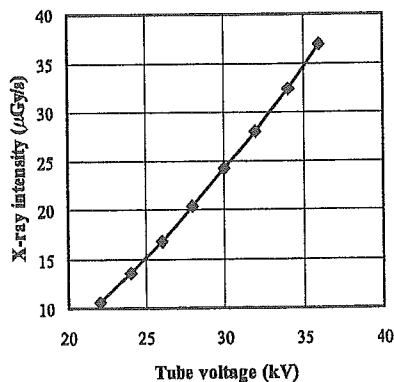


Fig. 3: X-ray intensity at 1.0 m from the x-ray source according to changes in the tube voltage.

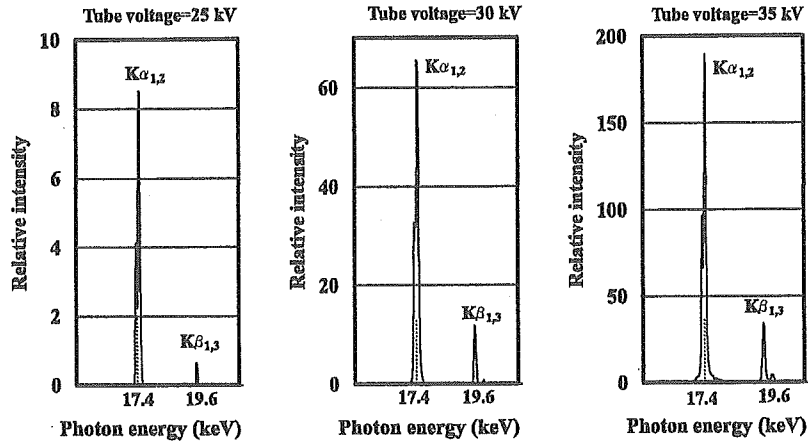


Fig. 4: X-ray spectra from the molybdenum target measured using a transmission type spectrometer with a lithium fluoride curved crystal.

increased. In this measurement, the intensity with a tube voltage of 30 kV and a current of  $100 \mu\text{A}$  was  $24.2 \mu\text{Gy/s}$  at 1.0 m from the source.

### 3.2 X-ray spectra

First, x-ray spectra were measured using a transmission-type spectrometer with a lithium fluoride curved crystal 0.5 mm in thickness. The x-ray intensities of the spectra were detected by an imaging plate of the CR system<sup>18</sup> (Konica Minolta Regius 150) with a wide dynamic range, and relative x-ray intensity was calculated from Dicom original digital data corresponding to x-ray intensity. Figure 4 shows measured spectra from the molybdenum target. We observed clean K lines, while bremsstrahlung

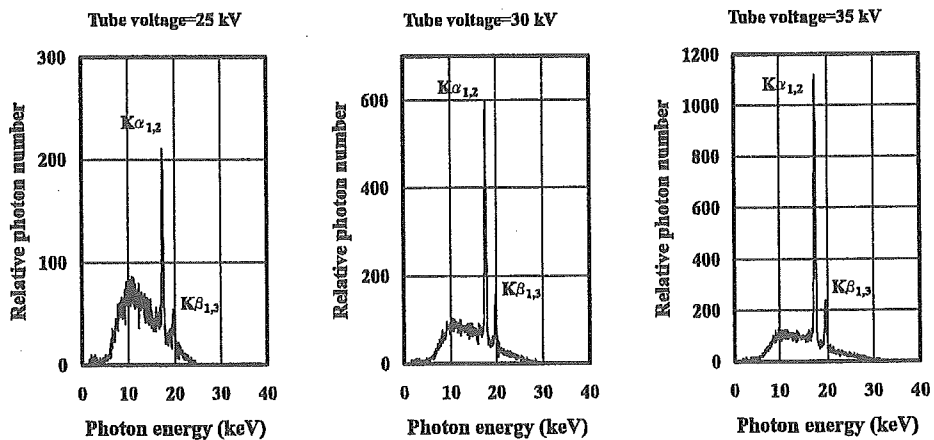


Fig. 5: X-ray spectra from the molybdenum target measured using a cadmium telluride detector.

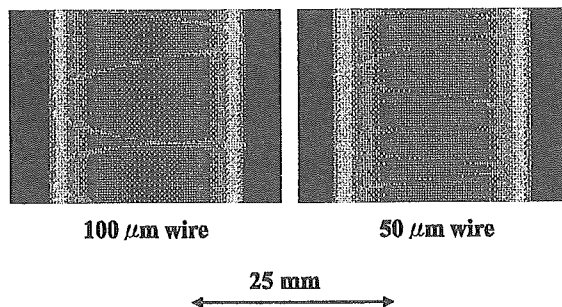


Fig. 6: Radiograms of tungsten wires of 50 and 100  $\mu\text{m}$  in diameter coiled around pipes made of polymethyl methacrylate. A 50- $\mu\text{m}$ -diameter wire could be observed.

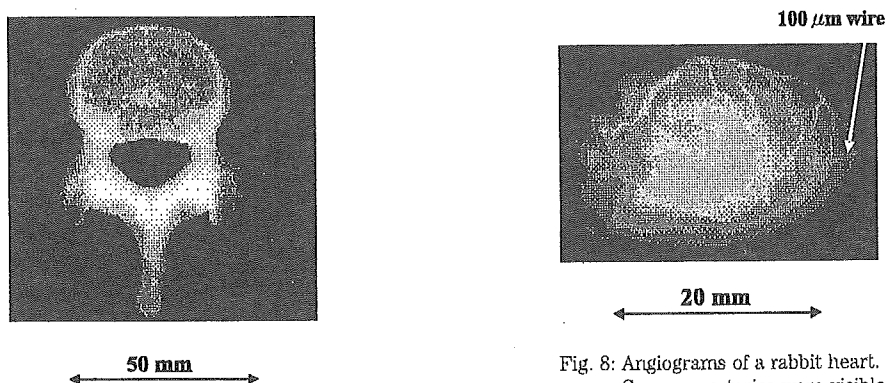


Fig. 7: Radiogram of a vertebra. Fine structure of the vertebra were visible.

Fig. 8: Angiograms of a rabbit heart. Coronary arteries were visible.

rays were hardly detected. The characteristic x-ray intensity substantially increased with increases in the tube voltage.

The measured spectra using a cadmium telluride detector are shown in Fig.5. Using the detector, we observed low intensity continuous x-rays. When the tube voltage was increased, both the characteristic x-ray intensity and the maximum photon energy increased.

#### 4. Radiography

The monochromatic radiography was performed by the CR system at 1.0 m from the x-ray source with the filter, and the tube voltage was 30 kV.

First, rough measurements of image resolution were made using wires. Figure 6 shows radiograms of tungsten wires coiled around pipes made of polymethyl methacrylate (PMMA). Although the image contrast increased with increases in the wire diameter, a 50- $\mu\text{m}$ -diameter wire could be observed.

A radiogram of a vertebra is shown in Fig. 7, and the fine structure of the vertebra was observed. Next, angiography was performed using iodine microspheres of 15  $\mu\text{m}$  in diameter. Figure 8 shows an angiogram of a rabbit heart, and we obtained high contrast images of coronary arteries and fine blood vessels.

## 5. Conclusions and Outlook

In summary, we developed a new characteristic x-ray generator with a molybdenum-target tube and measured clean molybdenum K lines using the crystal spectrometer. However, continuous x-rays were detected using the detector. In both measurements, the characteristic x-ray intensity increased with increases in the tube voltage, and monochromatic  $K\alpha$  lines were left by a zirconium filter. Because we could measure bremsstrahlung x-rays<sup>19</sup> from a transmission-type molybdenum target using the crystal, the bremsstrahlung intensity was low as compared with that obtained using conventional molybdenum tubes.

In this preliminary experiment, although the maximum tube voltage and current were 36 kV and 100  $\mu$ A, the voltage and current could be increased to 100 kV and 1.0 mA, respectively. Under the pulsed operation, the current can be increased to approximately 1 A without considering the target evaporation. Subsequently, the generator produced maximum number of characteristic photons was approximately  $1 \times 10^6$  photons/(cm<sup>2</sup> · s) at 1.0 m from the source, and the photon count rate can be increased easily by increasing the current.

Using this x-ray generator, because it is not easy to produce high-photon-energy K-series characteristic x-rays, we are very interested in increasing the energy by changing the electrode configuration between the target, cathode, and focusing electrodes.

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## References

1. R. Germer, "X-ray flash techniques," *J. Phys. E: Sci. Instrum.*, **12**, 336-350, 1979.
2. E. Sato, S. Kimura, S. Kawasaki, H. Isobe, K. Takahashi, Y. Tamakawa and T. Yanagisawa, "Repetitive flash x-ray generator utilizing a simple diode with a new type of energy-selective function," *Rev. Sci. Instrum.*, **61**, 2343-2348, 1990.
3. A. Shikoda, E. Sato, M. Sagae, T. Oizumi, Y. Tamakawa and T. Yanagisawa, "Repetitive flash x-ray generator having a high-durability diode driven by a two-cable-type line pulser," *Rev. Sci. Instrum.*, **65**, 850-856, 1994.
4. E. Sato, K. Takahashi, M. Sagae, S. Kimura, T. Oizumi, Y. Hayasi, Y. Tamakawa and T. Yanagisawa, "Sub-kilohertz flash x-ray generator utilizing a glass-enclosed cold-cathode triode," *Med. & Biol. Eng. & Comput.*, **32**, 289-294, 1994.
5. K. Takahashi, E. Sato, M. Sagae, T. Oizumi, Y. Tamakawa and T. Yanagisawa, "Fundamental study on a long-duration flash x-ray generator with a surface-discharge triode," *Jpn. J. Appl. Phys.*, **33**, pp. 4146-4151, 1994.
6. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, K. Takayama and H. Ido,

- "Quasi-monochromatic flash x-ray generator utilizing weakly ionized linear copper plasma," *Rev. Sci. Instrum.*, **74**, 5236-5240, 2003.
7. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, H. Obara, T. Ichimaru, K. Takayama and H. Ido, "Irradiation of intense characteristic x-rays from weakly ionized linear molybdenum plasma," *Jpn. J. Med. Phys.*, **23**, 123-131, 2003.
  8. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Sharp characteristic x-ray irradiation from weakly ionized linear plasma," *J. Electron Spectrosc. Related Phenom.*, **137-140**, 713-720, 2004.
  9. E. Sato, E. Tanaka, H. Mori, T. Kawai, S. Sato and K. Takayama, "Clean monochromatic x-ray irradiation from weakly ionized linear copper plasma," *Opt. Eng.*, **44**, 049002-1-6, 2005.
  10. E. Sato, M. Sagae, E. Tanaka, Y. Hayasi, R. Germer, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Quasi-monochromatic flash x-ray generator utilizing a disk-cathode molybdenum tube," *Jpn. J. Appl. Phys.*, **43**, 7324-7328, 2004.
  11. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Compact monochromatic flash x-ray generator utilizing a disk-cathode molybdenum tube," *Med. Phys.*, **32**, 49-54, 2005.
  12. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Inoue, A. Ogawa, S. Sato, K. Takayama and H. Ido, "High-speed K-edge angiography achieved with tantalum K-series characteristic x rays," *SPIE*, **5745**, 810-817, 2005.
  13. E. Sato, Y. Hayasi, R. Germer, K. Kimura, E. Tanaka, H. Mori, T. Kawai, T. Inoue, A. Ogawa, S. Sato, K. Takayama and H. Ido, "Enhanced K-edge plasma angiography achieved with tungsten  $K\alpha$  rays utilizing gadolinium-based contrast media," *SPIE*, **5920**, 592012-1-8, 2005.
  14. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Portable x-ray generator utilizing a cerium-target radiation tube for angiography," *J. Electron Spectrosc. Related Phenom.*, **137-140**, 699-704, 2004.
  15. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Demonstration of enhanced K-edge angiography using a cerium target x-ray generator," *Med. Phys.*, **31**, 3017-3021, 2004.
  16. E. Sato, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, H. Ojima, K. Takayama and H. Ido, "Quasi-monochromatic cerium flash angiography," *SPIE*, **5580**, 146-152, 2005.
  17. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Inoue, A. Ogawa, A. Yamadera, S. Sato, F. Ito, K. Takayama and H. Ido, "Variations in cerium x-ray spectra and enhanced K-edge angiography," *Jpn. J. Appl. Phys.*, **44**, 8204-8209, 2005.
  18. E. Sato, K. Sato and Y. Tamakawa, "Film-less computed radiography system for high-speed imaging," *Ann. Rep. Iwate Med. Univ. Sch. Lib. Arts and Sci.*, **35**, 13-23, 2000.
  19. M. Sagae, E. Sato, E. Tanaka, Y. Hayasi, R. Germer, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Quasi-monochromatic x-ray generator utilizing graphite cathode diode with transmission-type molybdenum target," *Jpn. J. Appl. Phys.*, **44**, 446-449, 2005.

## Measurement of Cerium X-ray Spectra Using a Cerium Oxide Powder Filter and Enhanced K-edge Angiography

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### Abstract

The cerium-target x-ray tube is useful in order to perform cone-beam K-edge angiography because K-series characteristic x-rays from the cerium target are absorbed effectively by iodine-based contrast media. The x-ray generator consists of a main controller and a unit with a high-voltage circuit and a fixed anode x-ray tube. The tube is a glass-enclosed diode with a cerium target and a 0.5-mm-thick beryllium window. The maximum tube voltage and current were 70 kV and 0.40 mA, respectively, and the focal-spot sizes were approximately 1×1 mm. Cerium K-series characteristic x-rays were left using a cerium oxide powder filter, and the x-ray intensity was 14.3 μGy/s at 1.0 m from the source with a tube voltage of 60 kV, a current of 0.40 mA, and an exposure time of 1.0 s. Angiography was performed with a computed radiography system using iodine-based microspheres 15 μm in diameter. In angiography of non-living animals, we observed fine blood vessels of approximately 100 μm with high contrasts.

**Keywords:** x-ray tube, cerium target, cerium oxide filter, powder filter, characteristic x-rays, K-edge angiography

### 1. Introduction

Flash x-ray generators are useful for performing high-speed radiography,<sup>1</sup> and several different generators with maximum photon energies of 150 keV<sup>2-5</sup> have been applied to biomedical radiography. By forming weakly ionized linear plasma<sup>6-9</sup> using a cold-cathode triode, we have succeeded in producing K-series characteristic x-rays of nickel and copper. Subsequently, we have developed super-fluorescent

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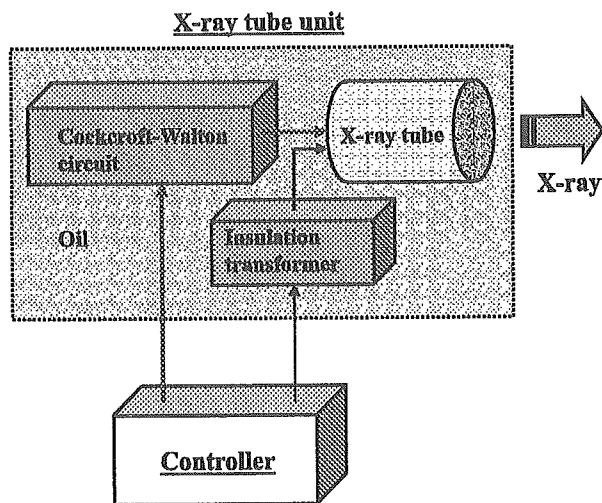


Fig. 1: Block diagram of the compact x-ray generator with a cerium-target radiation tube, which is used specially for K-edge angiography using iodine-based contrast media.

x-ray generator<sup>10-13</sup> to produce comparatively clean high-photon-energy characteristic x-rays of cerium and tungsten.

To produce steady state x-rays, synchrotrons generate high-dose-rate bremsstrahlung x-rays, and monochromatic parallel beams are formed using single crystals. In particular, x-rays of approximately 35 keV have been applied to perform enhanced K-edge angiography<sup>14,15</sup> and phase-contrast radiography,<sup>16,17</sup> including dark-field imaging using an analyzer crystal. Using these imaging, although the spatial resolution has been improved, it is difficult to increase the irradiation field due to the parallelity. Recently, we have developed a steady-state x-ray generator utilizing a cerium-target tube<sup>18-20</sup> and have demonstrated enhanced K-edge angiography utilizing a barium sulfate filter. In this research,  $K\alpha$  lines (34.6 keV) were left by absorbing  $K\beta$  lines (39.2 keV), and bremsstrahlung x-rays with photon energies lower than the barium K-edge (37.4 keV) were also observed. However, because cerium  $K\beta$  lines are also absorbed effectively by iodine, both  $K\alpha$  and  $K\beta$  lines should be selected to perform angiography. In the present research, we measured the x-ray spectra from a cerium-target tube using a new cadmium telluride detector, and performed a preliminary study on cone-beam K-edge angiography achieved with cerium characteristic x-rays using a cerium oxide powder filter.

## 2. Generator

Figure 1 shows the block diagram of the x-ray generator, which consists of a main controller and an x-ray tube unit with a Cockcroft-Walton circuit and a cerium-target tube. The tube voltage, the current, and the exposure time can be controlled by the controller. The main circuit for producing x-rays is illustrated in Fig. 2, and employed the Cockcroft-Walton circuit in order to decrease the dimensions of the tube unit. In the x-ray tube, the negative high-voltage is applied to the cathode electrode, and the anode (target) is connected to the tube unit case (ground potential) to cool the anode and the target effectively. The filament heating current is supplied by an AC power supply in the controller in

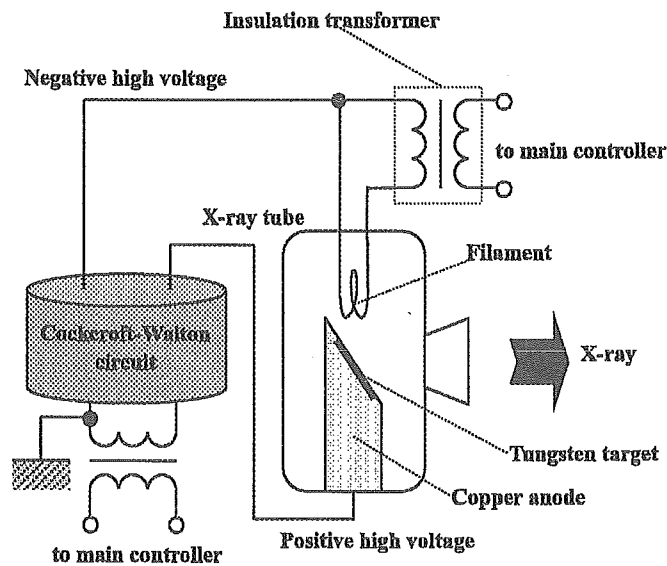


Fig. 2: Main circuit of the x-ray generator.

conjunction with an insulation transformer. In this experiment, the tube voltage applied was from 45 to 70 kV, and the tube current was regulated to within 0.40 mA (maximum current) by the filament temperature. The exposure time is controlled in order to obtain optimum x-ray intensity. Quasi-monochromatic x-rays are produced using a cerium oxide power filter with a surface density of 30 mg/cm<sup>2</sup>.

### 3. Characteristics

#### 3.1 X-ray Intensity

X-ray intensity was measured by a Victoreen 660 ionization chamber at 1.0 m from the x-ray source using the filter with an exposure time of 1.0 s (Fig. 3). At a constant tube current of 0.40 mA, the x-ray intensity increased when the tube voltage was increased. In this measurement, the intensity with a tube voltage of 60 kV and a current of 0.40 mA was 14.3  $\mu$ Gy/s at 1.0 m from the source.

#### 3.2 Focal spot

In order to measure images of the x-ray source after the filtration, we employed a pinhole camera with a hole diameter of 50  $\mu$ m (magnification ratio of 1:2) in conjunction with a Computed Radiography (CR)

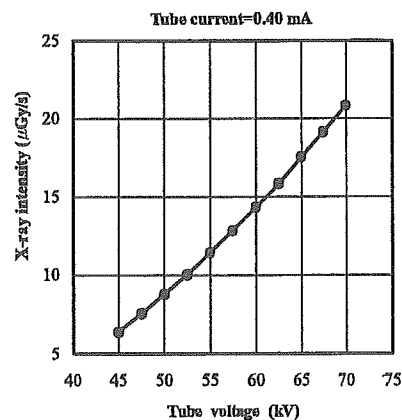


Fig. 3: X-ray intensity measured at 1.0 m from the x-ray source according to changes in the tube voltage.



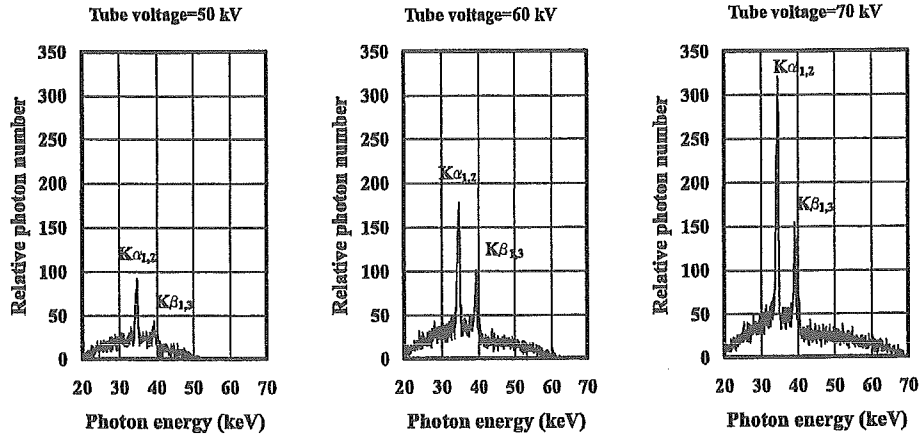


Fig. 4: X-ray spectra measured using a cadmium telluride detector with changes in the tube voltage.

system<sup>21</sup> with a sampling pitch of  $87.5 \mu\text{m}$ . When the tube voltage was increased, spot dimensions increased slightly and had values of approximately  $1 \times 1 \text{ mm}$ .

### 3.3 X-ray spectra

In order to measure x-ray spectra, we employed a cadmium telluride detector (XR-100T, Amptek Inc.) (Fig. 4). When the tube voltage was increased, the characteristic x-ray intensities of  $K\alpha$  and  $K\beta$  lines substantially increased, and both the maximum photon energy and the intensities of bremsstrahlung x-rays increased.

### 4. K-edge Angiography

Cerium is a rare earth element and has a high reactivity; however, the average photon energies of  $K\alpha$  and  $K\beta$  lines are 34.6 and 39.2 keV, respectively, and iodine contrast media with a K-absorption edge of

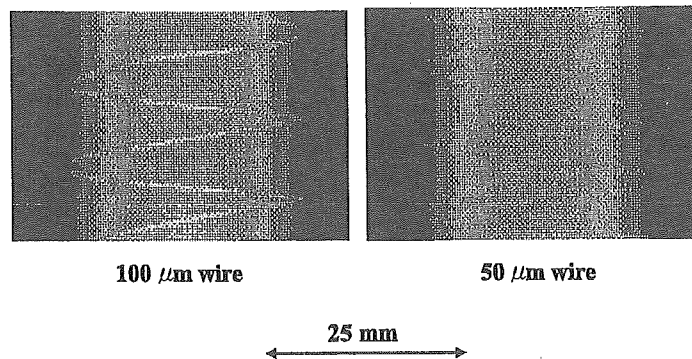


Fig. 5: Radiograms of tungsten wires coiled around PMMA rods.

33.2 keV absorb the lines easily. Therefore, blood vessels were observed with high contrasts.

The angiography was performed by the CR system<sup>21</sup> (Konica Regius 150) using the filter with a tube voltage of 60 kV, and the distance (between the x-ray source and the imaging plate) was 1.5 m. First, rough measurements of spatial resolution were made using wires. Figure 5 shows radiograms of tungsten wires coiled around rods made of polymethyl methacrylate. Although the image contrast decreased somewhat with decreases in the wire diameter, due to blurring of the image caused by the sampling pitch of 87.5  $\mu\text{m}$ , a 50- $\mu\text{m}$ -diameter wire could be observed.

An angiograms of a rabbit heart is shown in Fig. 6. This image was obtained using iodine microspheres of 15  $\mu\text{m}$  in diameter. Fine blood vessels in the coronary arteries in the heart were visible. Figure 7 shows an angiogram of a larger dog heart using iodine spheres, and blood vessels of approximately 100  $\mu\text{m}$  in diameter were visible.

### 5. Discussion

In summary, we employed an x-ray generator with a cerium-target tube and succeeded in producing cerium K-series characteristic x-rays, which can be absorbed easily by iodine-based contrast media. In the spectrum measurement, high-photon-energy bremsstrahlung x-rays beyond cerium K-edge (40.4 keV) were absorbed effectively.

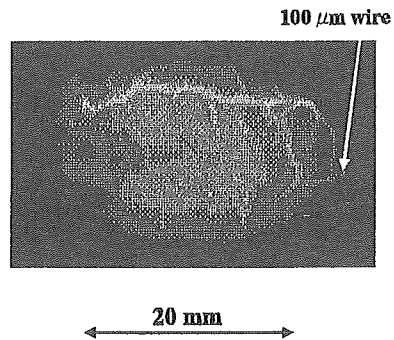


Fig. 6: Angiograms of an extracted rabbit heart using iodine microspheres.

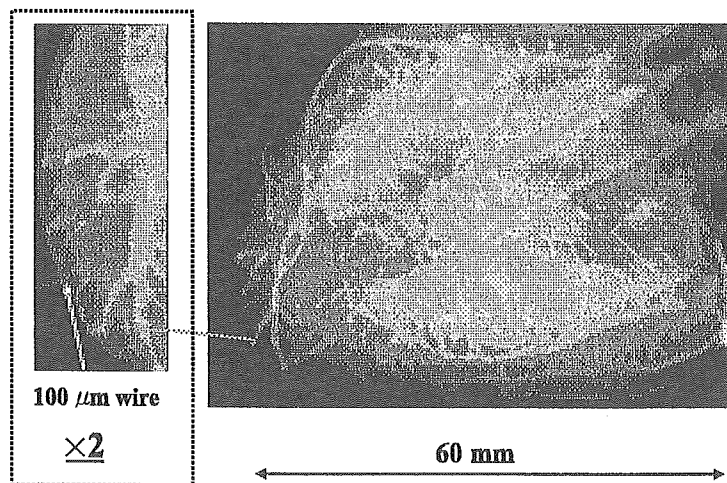


Fig. 7: Angiograms of an extracted dog heart using iodine microspheres.

In angiography, fine blood vessels were observed with high contrast with a spatial resolution of approximately 100  $\mu\text{m}$ ; the resolution was almost equal to the sampling pitch (87.5  $\mu\text{m}$ ) of the CR system. Therefore, the pith should be minimized, and magnification digital radiography including phase-contrast effect should be employed in order to improve the spatial resolution.

Although the cerium x-ray generator used in this research produces both the characteristic and the bremsstrahlung x-rays, bremsstrahlung intensity can be decreased effectively by considering the angle dependence without using the filter, since bremsstrahlung rays are not emitted in the opposite direction to that of electron trajectory. Subsequently, the generator produced maximum number of estimated characteristic photons was approximately  $5 \times 10^7$  photons / ( $\text{cm}^2 \cdot \text{s}$ ) at 1.0m from the source, and the photon count rate can be increased easily by improving the target.

### Acknowledgment

This work was supported by Grants-in-Aid for Scientific Research (13470154, 13877114, 16591181, and 16591222) and Advanced Medical Scientific Research from MECSSST, Health and Labor Sciences Research Grants (RAMT-nano-001, RHGTEFB-genome-005 and RHGTEFB-saisei-003), Grants from the Keiryō Research Foundation, The Promotion and Mutual Aid Corporation for Private Schools of Japan, Japan Science and Technology Agency (JST), and The New Energy and Industrial Technology Development Organization (NEDO, Industrial Technology Research Grant Program in '03).

### References

1. R. Germer, "X-ray flash techniques," *J. Phys. E: Sci. Instrum.*, **12**, 336-350, 1979.
2. E. Sato, S. Kimura, S. Kawasaki, H. Isobe, K. Takahashi, Y. Tamakawa and T. Yanagisawa, "Repetitive flash x-ray generator utilizing a simple diode with a new type of energy-selective function," *Rev. Sci. Instrum.*, **61**, 2343-2348, 1990.
3. A. Shikoda, E. Sato, M. Sagae, T. Oizumi, Y. Tamakawa and T. Yanagisawa, "Repetitive flash x-ray generator having a high-durability diode driven by a two-cable-type line pulser," *Rev. Sci. Instrum.*, **65**, 850-856, 1994.
4. E. Sato, K. Takahashi, M. Sagae, S. Kimura, T. Oizumi, Y. Hayasi, Y. Tamakawa and T. Yanagisawa, "Sub-kilohertz flash x-ray generator utilizing a glass-enclosed cold-cathode triode," *Med. & Biol. Eng. & Comput.*, **32**, 289-294, 1994.
5. K. Takahashi, E. Sato, M. Sagae, T. Oizumi, Y. Tamakawa and T. Yanagisawa, "Fundamental study on a long-duration flash x-ray generator with a surface-discharge triode," *Jpn. J. Appl. Phys.*, **33**, pp. 4146-4151, 1994.
6. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, K. Takayama and H. Ido, "Quasi-monochromatic flash x-ray generator utilizing weakly ionized linear copper plasma," *Rev. Sci. Instrum.*, **74**, 5236-5240, 2003.
7. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, H. Obara, T. Ichimaru, K. Takayama and H. Ido, "Irradiation of intense characteristic x-rays from weakly ionized linear molybdenum plasma," *Jpn. J. Med. Phys.*, **23**, 123-131, 2003.
8. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Sharp characteristic x-ray irradiation from weakly ionized linear plasma," *J. Electron*

- Spectrosc. Related Phenom.*, **137-140**, 713-720, 2004.
9. E. Sato, E. Tanaka, H. Mori, T. Kawai, S. Sato and K. Takayama, "Clean monochromatic x-ray irradiation from weakly ionized linear copper plasma," *Opt. Eng.*, **44**, 049002-1-6, 2005.
  10. E. Sato, M. Sagae, E. Tanaka, Y. Hayasi, R. Germer, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido: Quasi-monochromatic flash x-ray generator utilizing a disk-cathode molybdenum tube, *Jpn. J. Appl. Phys.*, **43**, 7324-7328, 2004.
  11. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Compact monochromatic flash x-ray generator utilizing a disk-cathode molybdenum tube," *Med. Phys.*, **32**, 49-54, 2005.
  12. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Inoue, A. Ogawa, S. Sato, K. Takayama and H. Ido, "High-speed K-edge angiography achieved with tantalum K-series characteristic x rays," *SPIE*, **5745**, 810-817, 2005.
  13. E. Sato, Y. Hayasi, R. Germer, K. Kimura, E. Tanaka, H. Mori, T. Kawai, T. Inoue, A. Ogawa, S. Sato, K. Takayama and H. Ido, "Enhanced K-edge plasma angiography achieved with tungsten K $\alpha$  rays utilizing gadolinium-based contrast media," *SPIE*, **5920**, 592012-1-8, 2005.
  14. H. Mori, K. Hyodo, E. Tanaka, M. U. Mohammed, A. Yamakawa, Y. Shinozaki, H. Nakazawa, Y. Tanaka, T. Sekka, Y. Iwata, S. Honda, K. Umetani, H. Ueki, T. Yokoyama, K. Tanioka, M. Kubota, H. Hosaka, N. Ishizawa and M. Ando, "Small-vessel radiography in situ with monochromatic synchrotron radiation," *Radiology*, **201**, 173-177, 1996.
  15. K. Hyodo, M. Ando, Y. Oku, S. Yamamoto, T. Takeda, Y. Itai, S. Ohtsuka, Y. Sugishita and J. Tada, "Development of a two-dimensional imaging system for clinical applications of intravenous coronary angiography using intense synchrotron radiation produced by a multipole wiggler," *J. Synchrotron Rad.*, **5**, 1123-1126, 1998.
  16. A. Momose, T. Takeda, Y. Itai and K. Hirano, "Phase-contrast x-ray computed tomography for observing biological soft tissues," *Nature Medicine*, **2**, 473-475, 1996.
  17. M. Ando, A. Maksimenko, H. Sugiyama, W. Pattanasiriwisawa, K. Hyodo and C. Uyama, "A simple x-ray dark- and bright- field imaging using achromatic Laue optics," *Jpn. J. Appl. Phys.*, **41**, L1016-L1018, 2002.
  18. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Portable x-ray generator utilizing a cerium-target radiation tube for angiography," *J. Electron Spectrosc. Related Phenom.*, **137-140**, 699-704, 2004.
  19. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Demonstration of enhanced K-edge angiography using a cerium target x-ray generator," *Med. Phys.*, **31**, 3017-3021, 2004.
  20. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Inoue, A. Ogawa, A. Yamadera, S. Sato, F. Ito, K. Takayama and H. Ido, "Variations in cerium x-ray spectra and enhanced K-edge angiography," *Jpn. J. Appl. Phys.*, **44**, 8204-8209, 2005.
  21. E. Sato, K. Sato and Y. Tamakawa, "Film-less computed radiography system for high-speed imaging," *Ann. Rep. Iwate Med. Univ. Sch. Lib. Arts and Sci.*, **35**, 13-23, 2000.

## Adrenomedullin: angiogenesis and gene therapy

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**Nagaya, Noritoshi, Hidezo Mori, Shinsuke Murakami, Kenji Kangawa, and Soichiro Kitamura.** Adrenomedullin: angiogenesis and gene therapy. *Am J Physiol Regul Integr Comp Physiol* 288: R1432–R1437, 2005; doi:10.1152/ajpregu.00662.2004.—Adrenomedullin (AM) is a potent, long-lasting vasodilator peptide that was originally isolated from human pheochromocytoma. AM signaling is of particular significance in endothelial cell biology since the peptide protects cells from apoptosis, promotes angiogenesis, and affects vascular tone and permeability. The angiogenic effect of AM is mediated by activation of Akt, mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2, and focal adhesion kinase in endothelial cells. Both AM and its receptor, calcitonin receptor-like receptor, are upregulated through a hypoxia-inducible factor-1-dependent pathway under hypoxic conditions. Thus AM signaling plays an important role in the regulation of angiogenesis in hypoxic conditions. Recently, we have developed a nonviral vector, gelatin. Positively charged gelatin holds negatively charged plasmid DNA in its lattice structure. DNA-gelatin complexes can delay gene degradation, leading to efficient gene transfer. Administration of AM DNA-gelatin complexes induces potent angiogenic effects in a rabbit model of hindlimb ischemia. Thus gelatin-mediated AM gene transfer may be a new therapeutic strategy for the treatment of tissue ischemia. Endothelial progenitor cells (EPCs) play an important role in endothelial regeneration. Interestingly, EPCs phagocytose ionically linked DNA-gelatin complexes in coculture, which allows nonviral gene transfer into EPCs. AM gene transfer into EPCs inhibits cell apoptosis and induces proliferation and migration, suggesting that AM gene transfer strengthens the therapeutic potential of EPCs. Intravenous administration of AM gene-modified EPCs regenerate pulmonary endothelium, resulting in improvement of pulmonary hypertension. These results suggest that in vivo and in vitro transfer of AM gene using gelatin may be applicable for intractable cardiovascular disease.

regeneration; endothelium; ischemia; pulmonary hypertension

ADRENOMEDULLIN (AM) IS A POTENT, long-lasting vasodilator peptide that was originally isolated from human pheochromocytoma (36). The peptide consists of 52 amino acids with an intramolecular disulfide bond, sharing slight homology with calcitonin gene-related peptide and amylin. Immunoreactive AM is detected in plasma and a variety of tissues including, blood vessels, heart, and lungs (19). Particularly, AM shows a variety of effects on the vasculature that include vasodilatation (23), regulation of permeability (16), inhibition of endothelial apoptosis (31), and promotion of angiogenesis (1, 35, 60). In addition, AM has protective effects against vascular injury, including oxidative stress (33, 69, 84). It is becoming clear that either activation or disruption of AM signaling might contribute to many pathological conditions, including hypertension (22), congestive heart failure (55), pulmonary hypertension (29), neoplastic growth (39), and inflammatory disease (59). To date, the major biological activities of AM in vitro and in vivo are 1) vasodilation, 2) diuresis and natriuresis, 3) positive inotropic effect, 4) inhibition of endothelial cell apoptosis, 5)

induction of angiogenesis, 6) inhibition of cardiomyocyte apoptosis, 7) suppression of aldosterone production, 8) anti-inflammatory activity, and 9) antioxidant activity. We and others have demonstrated that intravenous administration of AM decreases systemic and pulmonary arterial pressure and induces diuresis and natriuresis (47, 52, 65), suggesting that AM is involved in the regulation of vascular tone and body fluid. Subsequent studies have demonstrated beneficial hemodynamic effects and direct cardioprotective effects of AM infusion in the treatment of congestive heart failure (57, 61–64).

Until recently, only vascular endothelial growth factor (VEGF) (80), fibroblast growth factor (68), platelet-derived growth factor (37), and angiopoietin (74) were known to have profound angiogenic effects. More recently, however, the angiogenic potential of AM has attracted investigators' attention (35, 41, 59, 81). A previous study has shown that vascular abnormalities are present in homozygous AM knockout mice (70), suggesting that AM is essential for vascular morphogenesis. AM activates the PI3K/Akt-dependent pathway in vascular endothelial cells (58), which is considered to regulate multiple critical steps in angiogenesis, including endothelial cell survival, proliferation, migration, and capillary-like structure formation (27). These findings raise the possibility that AM plays a role in modulating angiogenesis and neovascular-

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ization. This review focused on the angiogenic effects of AM and the therapeutic potential of AM gene transfer for the treatment of intractable cardiovascular disease.

#### ENDOGENOUS AM PRODUCTION IN ISCHEMIC CONDITIONS

Hypoxia (14, 53) and cytokine production (73) in ischemic heart disease or septic shock, as well as shear stress (7) in hypertension and heart failure induce AM secretion by vascular cells (Fig. 1). We have shown that plasma AM level is increased in patients with acute myocardial infarction (40, 49), peripheral arterial occlusive disease (75), and congestive heart failure (28, 55). Tissue levels of AM peptide and mRNA are also markedly increased in ischemic myocardium (18, 50) and failing heart (8, 56, 78, 82). These findings suggest that expression of AM is upregulated under tissue ischemia and inflammation, both of which are associated with neovascularization. An *in vitro* study has demonstrated that AM is upregulated through a hypoxia-inducible factor-1 (HIF-1)-dependent pathway under hypoxic conditions (14). Thus hypoxia/HIF-1 is one of the most potent regulators of AM production (Fig. 1). A recent study has demonstrated that heterozygous AM knockout mice [AM(+/-)] show significantly less blood flow recovery with less collateral capillary development than their wild-type mice (20). Administration of AM promotes blood flow recovery and capillary formation in AM(+/-) mice. These findings suggest that endogenous AM may play an important role in the regulation of angiogenesis under ischemic conditions. Considering the angiogenic potency of AM, increased endogenous AM represents a compensatory mechanism as an angiogenic factor promoting neovascularization under hypoxic conditions.

#### ANGIOGENIC EFFECTS OF AM AND ITS SIGNALING PATHWAY

AM signaling is of particular significance in endothelial cell biology since the peptide protects cells from apoptosis (31), promotes angiogenesis (35, 60), and affects vascular tone (23). Angiogenesis is a multistep process that involves migration

and proliferation of endothelial cells, functional maturation of the newly assembled vessels, and remodeling of the extracellular matrix (26). Akt, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase 1/2 (ERK1/2), and focal adhesion kinase (p125FAK) play an important role in angiogenesis in endothelial cells. Kim et al. (35) demonstrated that AM activated Akt, MAPK/ERK1/2, and p125FAK in human umbilical vein endothelial cells (HUVECs), and produced increases in their DNA synthesis and migration. AM induced tube formation in HUVECs, and its effect was inhibited by pretreatment with a phosphatidylinositol 3'-kinase (PI3K) inhibitor or mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK)1/2 inhibitor. These findings suggest that AM exerts angiogenic activities through activation of Akt, MAPK, and p125FAK in endothelial cells (Fig. 1). *In vivo*, overexpression of AM augments collateral flow in ischemic tissues partly through activation of endothelial nitric oxide synthase (eNOS) (1). Earlier studies have shown that the vasodilatory effects of AM are mediated by cAMP/protein kinase in smooth muscle cells (SMCs) (23) and by the eNOS/NO pathway in endothelial cells (17). Thus AM-induced angiogenesis and vasodilation may synergistically improve blood perfusion in ischemic tissues.

Recently, a seven-transmembrane G-protein-coupled receptor, calcitonin receptor-like receptor (CRLR), and receptor activity modifying proteins (RAMPs) have been recognized as integral components of the AM signaling system (38, 43). CRLR has demonstrated the expression of the transcript predominantly in microvascular endothelial cells. This finding supports the view that CRLR is potentially a major mediator of the effects of AM on the vasculature. The effect of AM on CRLR is modified by RAMP2 and RAMP3. The angiogenic effect of AM is mediated by CRLR/RAMP2 and CRLR/RAMP3 receptors (Fig. 1). VEGF and AM act synergistically to induce angiogenic-related effects on endothelial cells *in vitro* (11). However, blocking antibodies to VEGF cannot significantly inhibit AM-induced capillary tube formation by

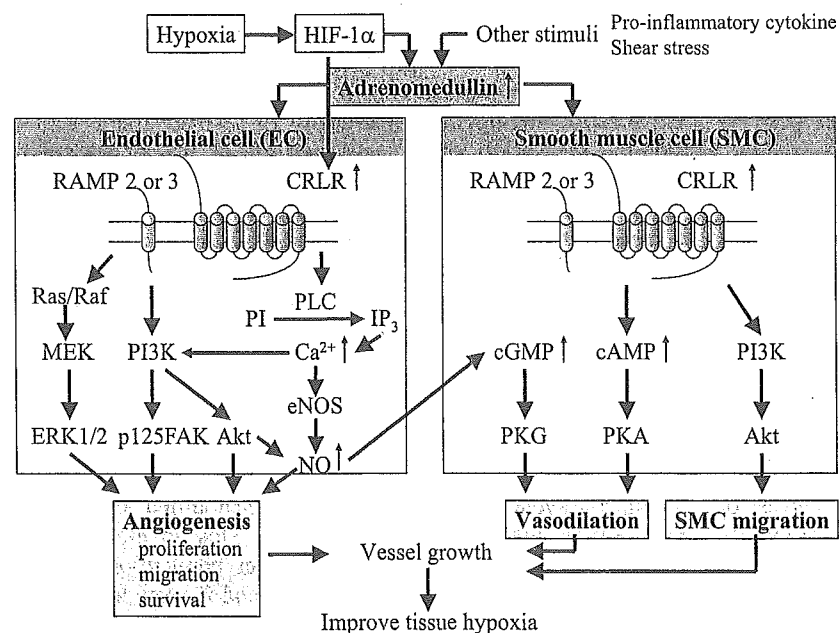


Fig. 1. Signaling pathway of adrenomedullin (AM) in vascular endothelial cells and smooth muscle cells. Both AM and calcitonin-receptor-like receptor (CRLR) are upregulated through a hypoxia-inducible factor-1 (HIF-1)-dependent pathway under hypoxic conditions. AM binds to CRLR modified by receptor-activity-modifying protein 2 (RAMP2) and RAMP3. AM induces angiogenesis through activation of Akt, MAPK, and p125FAK in endothelial cells. AM also induces SMC migration and vasodilation. These activities synergistically improve tissue ischemia. MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; p125FAK, focal adhesion kinase; PLC, phospholipase C; PI, phosphatidylinositol; IP<sub>3</sub>, inositol triphosphate; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; cGMP, guanosine 3',5'-cyclic monophosphate; PKG, protein kinase G; PKA, protein kinase A.

HUVECs, indicating that AM does not function indirectly through upregulation of VEGF. Interestingly, AM and CRLR are both upregulated under hypoxic conditions in microvascular endothelial cells, although expression of RAMPs is not activated by hypoxia in microvascular cells (54). The activity of the CRLR promoter under hypoxic conditions is regulated at least in part through hypoxia-responsive regulatory element binding transcription factor HIF-1. Thus the simultaneous transcriptional upregulation of CRLR and its ligand AM in endothelial cells might play a significant role in the vascular responses to hypoxia and ischemia by creating a potent survival loop.

SMCs are essential for the generation of functional and mature blood vessels (26). We demonstrated *in vivo* that intramuscular administration of AM increased the number of  $\alpha$ SMA-positive cells involved in the formation of vascular structures (25). *In vitro*, AM enhanced SMC migration, which was inhibited by wortmannin, a PI3K inhibitor. Recent studies using homozygous AM knockout mice have suggested that AM is essential for vascular morphogenesis (6, 21, 70). Taking these findings together, it is possible that AM contributes to vessel maturation through enhancement of SMC migration via a PI3K/Akt-dependent pathway (Fig. 1). This feature of AM-induced angiogenesis is different from VEGF-induced angiogenesis, which is not associated with vessel maturation.

In tumor cells, inflammation and hypoxia increase AM expression, and the elevated expression of AM is associated with tumor neovascularization in xenografted endometrial tumors and renal cell carcinoma (12, 86). AM also acts as a tumor cell survival factor underlying human carcinogenesis. Thus hypoxia-induced AM plays a part in tumor angiogenesis in conjunction with VEGF, and facilitates tumor growth under hypoxic conditions. As angiogenesis is an essential process in tumor-host interactions for tumor growth, maintenance, and metastasis, finding ways to regulate the action of AM may provide a new avenue for developing anticancer therapy (16).

#### THERAPEUTIC ANGIOGENESIS

A variety of studies have demonstrated that AM gene delivery serves as therapeutic tool to protect the cardiovascular system, including the heart (9, 32, 85), kidney (83), and vasculature (2, 84). In this section, we describe the angiogenic potential of AM gene transfer using novel gene delivery systems:

**Nonviral gene transfer.** Peripheral vascular disease is a crucial health issue affecting an estimated 27 million people (5). Despite recent advances in medical interventions, the symptoms of some patients with critical limb ischemia fail to be controlled. Although gene therapy has been shown to be an effective approach for angiogenesis (10, 24, 72), it is still unsatisfactory because of the biohazard of viral vectors, low transfection efficiency, and premature tissue-targeting. Therefore, highly efficient and safe gene transfer is desirable. Recently, we developed a novel nonviral vector, gelatin hydrogel, which allows highly efficient and long-lasting gene transfer (13, 30, 81). Gelatin has been widely used as a carrier of protein because of its capacity to delay protein degradation (76, 77). Plasmid DNA is known to be negatively charged. Thus we used gelatin as a vector for gene therapy. Biodegradable gelatin was prepared from pig skin. The gelatin was characterized by

a spheroid shape with a diameter of  $\sim 30$   $\mu$ m, water content of 95% and an isoelectric point of 9 after swelling in water (76, 77). After 2-h incubation, positively charged gelatin held negatively charged plasmid DNA in its positively charged lattice structure. DNA particles are released from the gelatin through its degradation. As a result, DNA-gelatin complexes can delay gene degradation, leading to efficient gene transfer (13, 30, 44, 81).

We examined whether nonviral vector gelatin-mediated AM gene transfer induces therapeutic angiogenesis in a rabbit model of hindlimb ischemia (81). Seven days after intramuscular injection of AM DNA-gelatin complexes, there was intense AM immunoreactivity surrounding the gelatin in the skeletal muscles. AM production in the AM-gelatin group was enhanced compared with that in the naked AM DNA group, which received plasmid AM DNA alone. Unlike AM production in the naked AM group, AM overexpression in the AM-gelatin group lasted for longer than 2 wk. Importantly, AM DNA-gelatin complexes induced more potent angiogenic effects in a rabbit model of hindlimb ischemia than naked AM DNA, as evidenced by significant increases in histological capillary density, calf blood pressure ratio, and laser Doppler flow. These results suggest that the use of biodegradable gelatin as a nonviral vector augments AM expression and enhances AM-induced angiogenic effects. AM DNA-gelatin complexes were distributed mainly in connective tissues. It is interesting to speculate that the delay of gene degradation by gelatin may have been responsible for the highly efficient gene transfer. Thus gelatin-mediated AM gene transfer may be a new therapeutic strategy for the treatment of severe peripheral vascular disease.

**Cell-based gene transfer.** Recently, transplantation of stem cells or progenitor cells has been shown to regenerate a variety of tissues. Endothelial progenitor cells (EPCs) have been discovered in adult peripheral blood (4, 79). EPCs are mobilized from bone marrow into the peripheral blood in response to tissue ischemia or traumatic injury, migrate to sites of injured endothelium, and differentiate into mature endothelial cells *in situ* (15, 34). Transplantation of EPC induces therapeutic angiogenesis in the ischemic heart or limb (34, 42, 71). However, some patients are refractory to conventional cell therapy because of insufficient cell number, poor survival, or impaired differentiation. Thus a novel therapeutic strategy to enhance the angiogenic properties of EPCs is desirable. Considering the variety of protective effects of AM on vascular endothelial cells, we hypothesized that AM gene transfer into EPCs would strengthen the therapeutic potential of EPCs. Genetically modified EPCs may serve not only as a tissue-engineering tool to reconstruct the vasculature but also as a vehicle for gene delivery to injured endothelium.

Here, we present a new concept for cell-based gene delivery into the vasculature, consisting of three processes (44). First, positively charged gelatin is readily complexed with negatively charged plasmid DNA. Second, EPCs phagocytose ionically linked plasmid DNA-gelatin complexes in coculture, which allows nonviral gene transfer into EPCs with high efficiency. Third, intravenously administered gene-modified EPCs are incorporated into injured vascular beds. This novel gene delivery system has great advantages over conventional gene therapy; it is nonviral and noninvasive, and it provides highly efficient gene targeting into the vasculature. These benefits

may be achieved mainly by the capability of EPCs to phagocytose DNA-gelatin complexes and to migrate to sites of injured endothelium. Genetically modified EPCs markedly secreted AM into the culture medium, and AM overproduction lasted for more than 2 wk. The proliferative activity of AM DNA-transduced EPCs exceeded that of nontransduced EPCs. Furthermore, AM gene transfer inhibited apoptosis of EPCs in vivo and in vitro. Thus ex vivo AM gene transfer strengthened the therapeutic potential of EPCs.

Primary pulmonary hypertension (PPH) is a rare, but life-threatening disease characterized by progressive pulmonary hypertension, ultimately producing right ventricular failure and death (67). Median survival in patients with PPH is considered to be 2.8 years from the time of diagnosis. Thus novel and effective therapy is needed for the treatment of pulmonary hypertension. Because endothelial dysfunction may play a role in the pathogenesis of pulmonary hypertension such as PPH (3), pulmonary endothelial cells may be a therapeutic target for the treatment of pulmonary hypertension. We have demonstrated that administration of AM peptide decreases pulmonary vascular resistance in patients with PPH (45, 46, 48, 51). Thus we investigated the effects of AM gene-modified EPCs on pulmonary hypertension in rats (44). AM gene-transduced EPCs were similarly incorporated into the pulmonary vasculature. Immunohistochemical analyses demonstrated that the transplanted EPCs were of endothelial lineage and formed vascular structures. Intravenous administration of AM-expressing EPCs significantly decreased pulmonary vascular resistance compared with EPCs alone (−39%). Kaplan-Meier survival curves demonstrated that rats with pulmonary hypertension transplanted with AM-expressing EPCs had a significantly higher survival rate than those given culture medium or EPCs alone. These findings suggest that AM gene-modified EPCs using gelatin may serve not only as a tissue-engineering tool to reconstruct the pulmonary vasculature, but also as a vehicle for gene delivery to injured pulmonary endothelium. This hybrid cell-gene therapy may be applicable for intractable cardiovascular disease, including ischemic heart disease. Thus genetic manipulation of stem cells opens new avenues for regenerative medicine.

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#### REFERENCES

1. Abe M, Sata M, Nishimatsu H, Nagata D, Suzuki E, Terauchi Y, Kadowaki T, Minamino N, Kangawa K, Matsuo H, Hirata Y, and Nagai R. Adrenomedullin augments collateral development in response to acute ischemia. *Biochem Biophys Res Commun* 306: 10–15, 2003.
2. Agata J, Zhang JJ, Chao J, and Chao L. Adrenomedullin gene delivery inhibits neointima formation in rat artery after balloon angioplasty. *Regul Pept* 112: 115–120, 2003.
3. Archer S and Rich S. Primary pulmonary hypertension: a vascular biology and translational research “work in progress”. *Circulation* 102: 2781–2791, 2000.
4. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schattman G, and Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 275: 964–967, 1997.
5. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton JD, Gavin 3rd JR, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA. Prevention of Atherothrombotic, and Disease Network. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med* 163: 884–892, 2003.
6. Caron KM and Smithies O. Extreme hydrops fetalis and cardiovascular abnormalities in mice lacking a functional adrenomedullin gene. *Proc Natl Acad Sci USA* 98: 615–619, 2001.
7. Chun TH, Itoh H, Ogawa Y, Tamura N, Takaya K, Igaki T, Yamashita J, Doi K, Inoue M, Masatsugu K, Korenaga R, Ando J, and Nakao K. Shear stress augments expression of C-type natriuretic peptide and adrenomedullin. *Hypertension* 29: 1296–1302, 1997.
8. Cueille C, Pidoux E, de Vernejoul MC, Ventura-Clapier R, and Garel JM. Increased myocardial expression of RAMP1 and RAMP3 in rats with chronic heart failure. *Biochem Biophys Res Commun* 294: 340–346, 2002.
9. Dobrzynski E, Wang C, Chao J, and Chao L. Adrenomedullin gene delivery attenuates hypertension, cardiac remodeling, and renal injury in deoxycorticosterone acetate-salt hypertensive rats. *Hypertension* 36: 995–1001, 2000.
10. Feldman LJ, Steg PG, Zheng LP, Chen D, Kearney M, McGarr SE, Barry JJ, Dedieu JF, Perricaudet M, and Isner JM. Low-efficiency of percutaneous adenovirus-mediated arterial gene transfer in the atherosclerotic rabbit. *J Clin Invest* 95: 2662–2671, 1995.
11. Fernandez-Sauze S, Delfino C, Mabrouk K, Dussert C, Chinot O, Martin PM, Grisoli F, Ouafik L, and Boudouresque F. Effects of adrenomedullin on endothelial cells in the multistep process of angiogenesis: involvement of CRLR/RAMP2 and CRLR/RAMP3 receptors. *Int J Cancer* 108: 797–804, 2004.
12. Fujita Y, Mimata H, Nasu N, Nomura T, Nomura Y, and Nakagawa M. Involvement of adrenomedullin induced by hypoxia in angiogenesis in human renal cell carcinoma. *Int J Urol* 9: 285–295, 2002.
13. Fukunaka Y, Iwanaga K, Morimoto K, Kakemi M, and Tabata Y. Controlled release of plasmid DNA from cationized gelatin hydrogels based on hydrogel degradation. *J Control Release* 80: 333–343, 2002.
14. Garayoa M, Martinez A, Lee S, Pio R, An WG, Neckers L, Trepel J, Montuenga LM, Ryan H, Johnson R, Gassmann M, and Cuttitta F. Hypoxia-inducible factor-1 (HIF-1) up-regulates adrenomedullin expression in human tumor cell lines during oxygen deprivation: a possible promotion mechanism of carcinogenesis. *Mol Endocrinol* 14: 848–862, 2000.
15. Gill M, Dias S, Hattori K, Rivera ML, Hicklin D, Witte L, Girardi L, Yurt R, Himel H, and Rafii S. Vascular trauma induces rapid but transient mobilization of VEGFR2(+)/AC133(+) endothelial precursor cells. *Circ Res* 88: 167–174, 2001.
16. Hippenstiel S, Witzenrath M, Schmeck B, Hocke A, Krisp M, Krull M, Seybold J, Seeger W, Rascher W, Schutte H, and Suttorp N. Adrenomedullin reduces endothelial hyperpermeability. *Circ Res* 91: 618–625, 2002.
17. Hirata Y, Hayakawa H, Suzuki Y, Suzuki E, Ikenouchi H, Kohmoto O, Kimura K, Kitamura K, Eto T, Kangawa K, Matsuo H, and Omata M. Mechanisms of adrenomedullin-induced vasodilation in the rat kidney. *Hypertension* 25: 790–795, 1995.
18. Hofbauer KH, Jensen BL, Kurtz A, and Sandner P. Tissue hypoxigenation activates the adrenomedullin system in vivo. *Am J Physiol Regul Integr Comp Physiol* 278: R513–R519, 2000.
19. Ichiki Y, Kitamura K, Kangawa K, Kawamoto M, Matsuo H, and Eto T. Distribution and characterization of immunoreactive adrenomedullin in human tissue and plasma. *FEBS Lett* 338: 6–10, 1994.
20. Iimuro S, Shindo T, Moriyama N, Amaki T, Niu P, Takeda N, Iwata H, Zhang Y, Ebihara A, and Nagai R. Angiogenic effects of adrenomedullin in ischemia and tumor growth. *Circ Res* 95: 415–423, 2004.
21. Imai Y, Shiindo T, Maemura K, Kurihara Y, Nagai R, and Kurihara H. Evidence for the physiological and pathological roles of adrenomedullin from genetic engineering in mice. *Ann NY Acad Sci* 947: 26–33, 2001.
22. Ishimitsu T, Nishikimi T, Saito Y, Kitamura K, Eto T, Kangawa K, Matsuo H, Omae T, and Matsuoka H. Plasma levels of adrenomedullin, a newly identified hypotensive peptide, in patients with hypertension and renal failure. *J Clin Invest* 94: 2158–2161, 1994.
23. Ishizaka Y, Ishizaka Y, Tanaka M, Kitamura K, Kangawa K, Minamino N, Matsuo H, and Eto T. Adrenomedullin stimulates cyclic AMP formation in rat vascular smooth muscle cells. *Biochem Biophys Res Commun* 200: 642–646, 1994.



24. Isner JM, Pieczek A, Schainfeld R, Blair R, Haley L, Asahara T, Rosenfield K, Razvi S, Walsh K, and Symes JF. Clinical evidence of angiogenesis after arterial gene transfer of phVEGF165 in patient with ischemic limb. *Lancet* 348: 370–374, 1996.
25. Iwase T, Nagaya N, Fujii T, Itoh T, Ishibashi-Ueda H, Yamagishi M, Miyatake K, Matsumoto T, Kitamura S, and Kangawa K. Adrenomedullin enhances angiogenic potency of bone marrow transplantation in a rat model of hindlimb ischemia. *Circulation* 111: 356–362, 2005.
26. Jain RK. Molecular regulation of vessel maturation. *Nat Med* 9: 685–693, 2003.
27. Jiang BH, Zheng JZ, Aoki M, and Vogt PK. Phosphatidylinositol 3-kinase signaling mediates angiogenesis and expression of vascular endothelial growth factor in endothelial cells. *Proc Natl Acad Sci USA* 97: 1749–1753, 2000.
28. Jougasaki M, Wei CM, McKinley LJ, and Burnett JC Jr. Elevation of circulating and ventricular adrenomedullin in human congestive heart failure. *Circulation* 92: 286–289, 1995.
29. Kakishita M, Nishikimi T, Okano Y, Satoh T, Kyotani S, Nagaya N, Fukushima K, Nakanishi N, Takishita S, Miyata A, Kangawa K, Matsuo H, and Kunieda T. Increased plasma levels of adrenomedullin in patients with pulmonary hypertension. *Clin Sci (Lond)* 96: 33–39, 1999.
30. Kasahara H, Tanaka E, Fukuyama N, Sato E, Sakamoto H, Tabata Y, Ando K, Iseki H, Shinozaki Y, Kimura K, Kuwabara E, Koide S, Nakazawa H, and Mori H. Biodegradable gelatin hydrogel potentiates the angiogenic effect of fibroblast growth factor 4 plasmid in rabbit hindlimb ischemia. *J Am Coll Cardiol* 41: 1056–1062, 2003.
31. Kato H, Shichiri M, Marumo F, and Hirata Y. Adrenomedullin as an autocrine/paracrine apoptosis survival factor for rat endothelial cells. *Endocrinology* 138: 2615–2620, 1997.
32. Kato K, Yin H, Agata J, Yoshida H, Chao L, and Chao J. Adrenomedullin gene delivery attenuates myocardial infarction and apoptosis after ischemia and reperfusion. *Am J Physiol Heart Circ Physiol* 285: H1506–H1514, 2003.
33. Kawai J, Ando K, Tojo A, Shimosawa T, Takahashi K, Onozato ML, Yamasaki M, Ogita T, Nakaoka T, and Fujita T. Endogenous adrenomedullin protects against vascular response to injury in mice. *Circulation* 109: 1147–1153, 2004.
34. Kawamoto A, Gwon HC, Iwaguro H, Yamaguchi JJ, Uchida S, Masuda H, Silver M, Ma H, Kearney M, Isner JM, and Asahara T. Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia. *Circulation* 103: 634–637, 2001.
35. Kim W, Moon SO, Sung MJ, Kim SH, Lee S, So JN, and Park SK. Angiogenic role of adrenomedullin through activation of Akt, mitogen-activated protein kinase, and focal adhesion kinase in endothelial cells. *FASEB J* 13: 1937–1939, 2003.
36. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, and Eto T. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* 192: 553–560, 1993.
37. Marx M, Perlmutter RA, and Madri JA. Modulation of platelet-derived growth factor receptor expression in microvascular endothelial cells during in vitro angiogenesis. *J Clin Invest* 93: 131–139, 1994.
38. McLatchie LM, Fraser NJ, Main MJ, Wise A, Brown J, Thompson N, Solari R, Lee MG, and Foord SM. RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor. *Nature* 393: 333–339, 1998.
39. Miller MJ, Martinez A, Unsworth EJ, Thiele CJ, Moody TW, Elsasser T, and Cuttitta F. Adrenomedullin expression in human tumor cell lines. Its potential role as an autocrine growth factor. *J Biol Chem* 271: 23345–23351, 1996.
40. Miyao Y, Nishikimi T, Goto Y, Miyazaki S, Daikoku S, Morii I, Matsumoto T, Takishita S, Miyata A, Matsuo H, Kangawa K, and Nonogi H. Increased plasma adrenomedullin levels in patients with acute myocardial infarction in proportion to the clinical severity. *Heart* 79: 39–44, 1998.
41. Miyashita K, Itoh H, Sawada N, Fukunaga Y, Sone M, Yamahara K, Yurugi-Kobayashi T, Park K, and Nakao K. Adrenomedullin provokes endothelial Akt activation and promotes vascular regeneration both in vitro and in vivo. *FEBS Lett* 544: 86–92, 2003.
42. Murohara T, Ikeda H, Duan J, Shintani S, Sasaki K, Eguchi H, Onitsuka I, Matsui K, and Imaizumi T. Transplanted cord blood-derived endothelial precursor cells augment postnatal neovascularization. *J Clin Invest* 105: 1527–1536, 2000.
43. Nagae T, Mukoyama M, Sugawara A, Mori K, Yahata K, Kasahara M, Suganami T, Makino H, Fujinaga Y, Yoshioka T, Tanaka I, and Nakao K. Rat receptor-activity-modifying proteins (RAMPs) for adrenomedullin/CGRP receptor: cloning and upregulation in obstructive nephropathy. *Biochem Biophys Res Commun* 270: 89–93, 2000.
44. Nagaya N, Kangawa K, Kanda M, Uematsu M, Horio T, Fukuyama N, Hino J, Harada-Shiba M, Okumura H, Tabata Y, Mochizuki N, Chiba Y, Nishioka K, Miyatake K, Asahara T, Hara H, and Mori H. Hybrid cell-gene therapy for pulmonary hypertension based on phagocytosing action of endothelial progenitor cells. *Circulation* 108: 889–895, 2003.
45. Nagaya N, Kyotani S, Uematsu M, Ueno K, Oya H, Nakanishi N, Shirai M, Mori H, Miyatake K, and Kangawa K. Effects of adrenomedullin inhalation on hemodynamics and exercise capacity in patients with idiopathic pulmonary arterial hypertension. *Circulation* 109: 351–356, 2004.
46. Nagaya N, Miyatake K, Kyotani S, Nishikimi T, Nakanishi N, and Kangawa K. Pulmonary vasodilator response to adrenomedullin in patients with pulmonary hypertension. *Hypertens Res* 26 Suppl: S141–S146, 2003.
47. Nagaya N, Nishikimi T, Horio T, Yoshihara F, Kanazawa A, Matsuo H, and Kangawa K. Cardiovascular and renal effects of adrenomedullin in rats with heart failure. *Am J Physiol Regul Integr Comp Physiol* 276: R213–R218, 1999.
48. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Oya H, Kyotani S, Sakamaki F, Ueno K, Nakanishi N, Miyatake K, and Kangawa K. Hemodynamic and hormonal effects of adrenomedullin in patients with pulmonary hypertension. *Heart* 84: 653–658, 2000.
49. Nagaya N, Nishikimi T, Uematsu M, Yoshitomi Y, Miyao Y, Miyazaki S, Goto Y, Kojima S, Kuramochi M, Matsuo H, Kangawa K, and Nonogi H. Plasma adrenomedullin as an indicator of prognosis after acute myocardial infarction. *Heart* 81: 483–487, 1999.
50. Nagaya N, Nishikimi T, Yoshihara F, Horio T, Morimoto A, and Kangawa K. Cardiac adrenomedullin gene expression and peptide accumulation after acute myocardial infarction in rats. *Am J Physiol Regul Integr Comp Physiol* 278: R1019–R1026, 2000.
51. Nagaya N, Okumura H, Uematsu M, Shimizu W, Ono F, Shirai M, Mori H, Miyatake K, and Kangawa K. Repeated inhalation of adrenomedullin ameliorates pulmonary hypertension and survival in monocrotaline rats. *Am J Physiol Heart Circ Physiol* 285: H2125–H2131, 2003.
52. Nagaya N, Satoh T, Nishikimi T, Uematsu M, Furuichi S, Sakamaki F, Oya H, Kyotani S, Nakanishi N, Goto Y, Masuda Y, Miyatake K, and Kangawa K. Hemodynamic, renal, and hormonal effects of adrenomedullin infusion in patients with congestive heart failure. *Circulation* 101: 498–503, 2000.
53. Nakayama M, Takahashi K, Murakami O, Shirato K, and Shibahara S. Induction of adrenomedullin by hypoxia and cobalt chloride in human colorectal carcinoma cells. *Biochem Biophys Res Commun* 243: 514–517, 1998.
54. Nikitenko LL, Smith DM, Bicknell R, and Rees MC. Transcriptional regulation of the CRLR gene in human microvascular endothelial cells by hypoxia. *FASEB J* 17: 1499–501, 2003.
55. Nishikimi T, Saito Y, Kitamura K, Ishimitsu T, Eto T, Kangawa K, Matsuo H, Omae T, and Matsuoka H. Increased plasma levels of adrenomedullin in patients with heart failure. *J Am Coll Cardiol* 26: 1424–1431, 1995.
56. Nishikimi T, Tadokoro K, Mori Y, Wang X, Akimoto K, Yoshihara F, Minamino N, Kangawa K, and Matsuoka H. Ventricular adrenomedullin system in the transition from LVH to heart failure in rats. *Hypertension* 41: 512–518, 2003.
57. Nishikimi T, Yoshihara F, Horinaka S, Kobayashi N, Mori Y, Tadokoro K, Akimoto K, Minamino N, Kangawa K, and Matsuoka H. Chronic administration of adrenomedullin attenuates transition from left ventricular hypertrophy to heart failure in rats. *Hypertension* 42: 1034–1041, 2003.
58. Nishimatsu H, Suzuki E, Nagata D, Moriyama N, Satonaka H, Walsh K, Sata M, Kangawa K, Matsuo H, Goto A, Kitamura T, and Hirata Y. Adrenomedullin induces endothelium-dependent vasorelaxation via the phosphatidylinositol 3-kinase/Akt-dependent pathway in rat aorta. *Circ Res* 89: 63–70, 2001.
59. Nishio K, Akai Y, Murao Y, Doi N, Ueda S, Tabuse H, Miyamoto S, Dohi K, Minamino N, Shoji H, Kitamura K, Kangawa K, and Matsuo H. Increased plasma concentrations of adrenomedullin correlate with relaxation of vascular tone in patients with septic shock. *Crit Care Med* 25: 953–957, 1997.

60. Oehler MK, Hague S, Rees MC, and Bicknell R. Adrenomedullin promotes formation of xenografted endometrial tumors by stimulation of autocrine growth and angiogenesis. *Oncogene* 21: 2815–2821, 2002.
61. Okumura H, Nagaya N, Itoh T, Okano I, Hino J, Mori K, Tsukamoto Y, Ishibashi-Ueda H, Miwa S, Tambara K, Toyokuni S, Yutani C, and Kangawa K. Adrenomedullin infusion attenuates myocardial ischemia/reperfusion injury through the phosphatidylinositol 3-kinase/Akt-dependent pathway. *Circulation* 109: 242–248, 2004.
62. Rademaker MT, Cameron VA, Charles CJ, Lainchbury JG, Nicholls MG, and Richards AM. Adrenomedullin and heart failure. *Regul Pept* 112: 51–60, 2003.
63. Rademaker MT, Charles CJ, Cooper GJ, Coy DH, Espiner EA, Lewis LK, Nicholls MG, and Richards AM. Combined angiotensin-converting enzyme inhibition and adrenomedullin in an ovine model of heart failure. *Clin Sci (Lond)* 102: 653–660, 2002.
64. Rademaker MT, Charles CJ, Espiner EA, Nicholls MG, and Richards AM. Long-term adrenomedullin administration in experimental heart failure. *Hypertension* 40: 667–672, 2002.
65. Rademaker MT, Charles CJ, Lewis LK, Yandle TG, Cooper GJ, Coy DH, Richards AM, and Nicholls MG. Beneficial hemodynamic and renal effects of adrenomedullin in an ovine model of heart failure. *Circulation* 96: 1983–1990, 1997.
66. Ribatti D, Guidolin D, Conconi MT, Nico B, Baiguera S, Parnigotto PP, Vacca A, and Nussdorfer GG. Vinblastine inhibits the angiogenic response induced by adrenomedullin in vitro and in vivo. *Oncogene* 22: 6458–6461, 2003.
67. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, Levy PC, Reid LM, Vreim CE, and Williams GW. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 107: 216–223, 1987.
68. Schweigerer L, Neufeld G, Friedman J, Abraham JA, Fiddes JC, and Gospodarowicz D. Capillary endothelial cells express basic fibroblast growth factor, a mitogen that promotes their own growth. *Nature* 325: 257–259, 1987.
69. Shimosawa T, Shibagaki Y, Ishibashi K, Kitamura K, Kangawa K, Kato S, Ando K, and Fujita T. Adrenomedullin, an endogenous peptide, counteracts cardiovascular damage. *Circulation* 105:106–111, 2002.
70. Shindo T, Kurihara Y, Nishimatsu H, Moriyama N, Kakoki M, Wang Y, Imai Y, Ebihara A, Kuwaki T, Ju KH, Minamino N, Kangawa K, Ishikawa T, Fukuda M, Akimoto Y, Kawakami H, Imai T, Morita H, Yazaki Y, Nagai R, Hirata Y, and Kurihara H. Vascular abnormalities and elevated blood pressure in mice lacking adrenomedullin gene. *Circulation* 104: 1964–1971, 2001.
71. Shintani S, Murohara T, Ikeda H, Ueno T, Sasaki K, Duan J, and Imaizumi T. Augmentation of postnatal neovascularization with autologous bone marrow transplantation. *Circulation* 103: 897–903, 2001.
72. St George JA. Gene therapy progress and prospects: adenoviral vectors. *Gene Ther* 10: 1135–1141, 2003.
73. Sugo S, Minamino N, Shoji H, Kangawa K, Kitamura K, Eto T, and Matsuo H. Interleukin-1, tumor necrosis factor and lipopolysaccharide additively stimulate production of adrenomedullin in vascular smooth muscle cells. *Biochem Biophys Res Commun* 207: 25–32, 1995.
74. Suri C, Jones PF, Patan S, Bartunkova S, Maisonpierre PC, Davis S, Sato TN, and Yancopoulos GD. Requisite role of angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis. *Cell* 87: 1171–1180, 1996.
75. Suzuki Y, Horio T, Hayashi T, Nonogi H, Kitamura K, Eto T, Kangawa K, and Kawano Y. Plasma adrenomedullin concentration is increased in patients with peripheral arterial occlusive disease associated with vascular inflammation. *Regul Pept* 118: 99–104, 2004.
76. Tabata Y and Ikada Y. Macrophage activation through phagocytosis of muramyl dipeptide encapsulated in gelatin microspheres. *J Pharm Pharmacol* 39: 698–704, 1987.
77. Tabata Y, Nagano A, and Ikada Y. Biodegradation of hydrogel carrier incorporating fibroblast growth factor. *Tissue Eng* 5: 127–138, 1999.
78. Tadokoro K, Nishikimi T, Mori Y, Wang X, Akimoto K, and Matsuo H. Altered gene expression of adrenomedullin and its receptor system and molecular forms of tissue adrenomedullin in left ventricular hypertrophy induced by malignant hypertension. *Regul Pept* 112: 71–78, 2003.
79. Takahashi T, Kalka C, Masuda H, Chen D, Silver M, Kearney M, Magner M, Isner JM, and Asahara T. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. *Nat Med* 5: 434–438, 1999.
80. Takeshita S, Zheng LP, Brogi E, Kearney M, Pu LQ, Bunting S, Ferrara N, Symes JF, and Isner JM. Therapeutic angiogenesis. A single intra-arterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model. *J Clin Invest* 93: 662–670, 1994.
81. Tokunaga N, Nagaya N, Shirai M, Tanaka E, Ishibashi-Ueda H, Harada-Shiba M, Kanda M, Ito T, Shimizu W, Tabata Y, Uematsu M, Nishigami K, Sano S, Kangawa K, and Mori H. Adrenomedullin gene transfer induces therapeutic angiogenesis in a rabbit model of chronic hind limb ischemia: benefits of a novel nonviral vector, gelatin. *Circulation* 109: 526–531, 2004.
82. Totsune K, Takahashi K, Mackenzie HS, Murakami O, Arihara Z, Sone M, Mouri T, Brenner BM, and Ito S. Increased gene expression of adrenomedullin and adrenomedullin-receptor complexes, receptor-activity modifying protein (RAMP)2 and calcitonin-receptor-like receptor (CRLR) in the hearts of rats with congestive heart failure. *Clin Sci (Lond)* 99: 541–546, 2000.
83. Wang C, Dobrzynski E, Chao J, and Chao L. Adrenomedullin gene delivery attenuates renal damage and cardiac hypertrophy in Goldblatt hypertensive rats. *Am J Physiol Renal Physiol* 280: F964–F971, 2001.
84. Yamasaki M, Kawai J, Nakaoka T, Ogita T, Tojo A, and Fujita T. Adrenomedullin overexpression to inhibit cuff-induced arterial intimal formation. *Hypertension* 41: 302–307, 2003.
85. Yin H, Chao L, and Chao J. Adrenomedullin protects against myocardial apoptosis after ischemia/reperfusion through activation of Akt-GSK signaling. *Hypertension* 43: 109–116, 2004.
86. Zudaire E, Martinez A, and Cuttitta F. Adrenomedullin and cancer. *Regul Pept* 112: 175–183, 2003.

## シンクロトロンにかわる医用単色X線装置の開発と応用

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### Development of monochromatic x-ray generators instead of a synchrotron and applications

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#### 1. はじめに

X線レーザーの研究は世界各国で行われており、レーザー発振のためのさまざまな方法が考案されている<sup>1-4)</sup>。レーザーは誘導放出による光の増幅を意味するが、誘導放出によってはフォトンエネルギーを高めることは難しい。このことから誘導放出とは異なるが、自由電子レーザー<sup>5)</sup>による方法が考案され、研究されている。人体をも撮影できるハードX線レーザーの発振はノーベル賞に値するといわれているが、まだそれらの発生は報告されていない。したがって、もし仮にハードX線レーザーが定常的に発生できれば、医療における診断や治療に大きく貢献すると思われる。

シンクロトロンとモノクロリメーターを用いて発生する単色平行X線はヨウ素のKエッジ造影

6-8) や位相コントラスト撮影<sup>9-11)</sup>等に応用され、X線撮影上革命的な成果をあげている。特に、血管造影にはK吸収端が33.2 keVのヨウ素系造影剤が利用されるので、吸収端よりもわずかに高いフォトンエネルギーのX線は造影剤に効率良く吸収される。したがって、35 keV程度の単色平行X線は微小血管造影には非常に有用であることから、造影室はシンクロトロン施設内に設置されている。

マイクロフォーカスX線管を用いた輪郭強調X線位相コントラスト撮影はWilkins<sup>12)</sup>により考案された。最近、100  $\mu\text{m}$ 程度の小焦点モリブデン管とCRを用いた高精細マンモグラフィシステム<sup>13,14)</sup>がコニカミノルタから発売され、普及しつつある。X線撮像においてもデジタル化は進んでいるが、イメージングプレートを用いたコンピューターラジオグラフィ(CR)<sup>15)</sup>やフラットパネルディテクター(FPD)はX線フィルムと比較して空間分解能が劣るので、拡大撮影による分解能の向上は必須である。さらに拡大により被写体からの散乱線の影響が低減され、位相コントラストの効果が加わる。このことから筆者等はデジタル拡大撮影の微小血管造影への応用を試み、良好な成果を得ている。

筆者等は単色X線撮影を行うため、エネルギー選択式のFPDの開発も行っているが、本稿では、近年開発した、種々のX線装置の特性やCRにより撮影した画像について簡単に説明する。

## 2. 低フォトンエネルギープラズマX線装置

低フォトンエネルギーの弱電離プラズマX線装置<sup>16-20)</sup>はハードX線レーザーの基礎研究のために開発され、銅やニッケル等のK系列特性X線を出力させるのに有用である。Fig. 1のように200 nFのコンデンサーを50 kV程度に充電し、蓄積された電荷をX線管の陰極にトリガ電圧を印加することにより放電する。この装置では高エネルギー放電により弱電離プラズマを成長させ、これを線状に形成することにより、制動X線が吸収され、蛍光X線(特性X線)に変換される。吸収係数が不連続なことから特性線はプラズマを容易に透過するので、単色化フィルターを挿入しなくとも高線量率の準単色X線が発生する。加えて、KエッジフィルターによりK $\beta$ 線を吸収すれば、K $\alpha$ 線が得られる。X線管には長い棒状ターゲットが取付けてあり、1 mPa程度に連続排気される。

管電圧と電流は減衰振動となり、それらの最大値は充電電圧を高めることにより増加した。実験結果より、管電圧の最大値は充電電圧にほぼ匹敵し、最大管電流値は約15 kAであった。また熱蛍光線量計で測定した最大X線強度は線源から1.0 mの位置で1パルス当たり1.5 mGy程度であった。

X線スペクトルの測定には、厚さ0.5 mmのフッ化リチウム湾曲単結晶付の透過式分光器を用いた(Fig. 2)。実験ではクリーンなK系列特性X線が観測され、充電電圧の増加によりX線強度は著しく増加した。驚くことに、充電電圧が50 kVでは、高調波が観測された。

X線撮影には厚さ10  $\mu\text{m}$ のニッケルフィルターを用い、撮影距離と充電電圧はそれぞれ1.2 mと50 kVであった。写真はプラスチックの試験管からこぼれ落ちるプラスチック弾である(Fig. 3)。この装置のX線照射時間は約1  $\mu\text{s}$ であるため、完全静止画像が得られた。