UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GLENN VAN LANGENHOVE and
LEONIDAS DIAMANTOPOULOS

Appeal No. 2006-3202
Application No. 10/323,592

ON BRIEF

Before ADAMS, LINCK, and LEBOVITZ, Administrative Patent Judges.

LEBOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to methods of diagnosing the presence of inflamed atherosclerotic plaques by detecting elevated temperatures within the vessel lumen. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 134. We affirm-in-part, vacate-in-part, and remand to the Examiner.

Background

Plaque can develop in the blood vessels of the cardiovascular system. Specification, page 1, line 17. When plaque becomes inflamed and instable, it can rupture, causing “the patient to experience a myocardial infarction, thrombosis or other

traumatic and unwanted effects." Id., page 1, lines 19-21. The prior art has shown that inflamed plaques produce more heat than non-inflamed plaques. Id., page 1, line 26-page 2, line 6.

The instant application describes the finding that, when thermal measurements are taken from arteries with flowing blood, the differences recorded between inflamed and normal vessel regions are "much lower" than those observed in the prior art. Id., page 3, lines 6-10.

Discussion

Claim construction

Claims 1-20, 22-25, 27-41, and 43-50 are on appeal. Separate reasons for patentability have been provided for claim 30-33. Brief, page 16. Consequently, these claims stand or fall apart from claims 1-20, 22-25, 27-29, 34-41, and 43-50. We select claims 1[1] and 30 as representative of the claim groupings.

> 1. A method of diagnosing the presence of inflamed atherosclerotic plaque in a blood vessel of a subject, the method comprising:
> providing a temperature detection device which detects temperature at the inner vascular wall,
> introducing the temperature detection device into a blood vessel,
> determining a reference temperature value,
> measuring at least one first temperature value at the inner vascular wall,
> determining the difference between the first temperature value and the reference temperature value,
> and, where the difference is above zero but not more than 0.39°C, diagnosing the presence of inflamed atherosclerotic plaque in the blood vessel,
> wherein throughout the method the blood flow velocity in the blood vessel is at least 5 cm/s.

[1] Claim 1 in the Appendix to the Brief contained an error in not incorporating a claim amendment made April 4, 2005. The text of claim 1 which is reproduced here correctly incorporates the amendment.

30. A method of diagnosing the presence of inflamed atherosclerotic plaque in a blood vessel of a subject, the method comprising:
providing a temperature detection device which detects temperature at the inner vascular wall,
introducing the temperature detection device into a blood vessel,
determining a reference temperature value,
measuring at least one first temperature value at the inner vascular wall,
determining the difference between the first temperature value and the reference temperature value, and
diagnosing the presence of inflamed atherosclerotic plaque in the blood vessel where the difference is above zero but not more than 0.14°C.

Claim 1 involves five basic steps: 1) "introducing" a device to measure temperature into a blood vessel; 2) "determining" a reference temperature; 3) "measuring" the temperature of a region of the vessel wall ("inner vascular wall"); 4) "determining" the difference between the measured temperature and the "reference temperature"; and 5) diagnosing the presence of an inflamed plaque when the temperature difference is "above zero but not more than 0.39°C." The temperatures are recorded from a blood vessel having a blood flow velocity of "at least 5 cm/s."

Claim 30 is similarly constructed, but it does not require the presence of blood flow in the vessel. The inflamed plaque is diagnosed when the difference between the reference and vessel wall temperatures is "above zero but not more than 0.14°C."

Rejection under § 103

Claims 1-20, 22-25, 27-41, and 43-50 stand rejected under 35 U.S.C. § 103(a) as obvious over Casscells '261[2] in view of Nakano.[3]

[2] Casscells et al. (Cascells '261), U.S. Pat. No. 6,763,261, issued Jul. 13, 2004.
[3] Nakano et al. (Nakano), J. Nippon Med. Sch., 68:482-489, 2001.

Casscells '261 teaches "[m]ethods and devices . . . for detecting vulnerable atherosclerotic plaque, or plaque at risk of reducing blood flow in a vessel, by identifying a region of elevated temperature along a living vessel wall." Casscells '261, Abstract. "Vulnerable" or "at-risk" plaques are unstable atherosclerotic plaques which are susceptible to rupture. Id., column 1, line 57-column 2, line 40. "Rupture and/or thrombosis of an atherosclerotic plaque is the immediate cause of most myocardial infarctions and strokes." Id., column 1, lines 44-47.

Using both intravascular and non-invasive devices for measuring vessel wall temperature, Casscells '261 show that vulnerable plaques give off more heat than other vessel wall regions. As compared to unaffected regions, the temperature in vulnerable plaques is elevated in the range of about 0.2°C-5°C. Id., column 6, lines 23-30. "An important advantage of the present methods is that they assist the physician in diagnosing plaques at imminent risk of rupturing or occluding so that appropriate interventional steps may be taken to avert a possibly fatal cardiovascular event." Id., column 5, lines 39-44.

The Examiner argues that Casscells' '261 method meets the "providing," "introducing", "determining", and "measuring" requirements of claim 1 (see Answer, page 6, lines 7-13), but does not disclose the specific temperature range recited in claim 1 nor that the blood flow velocity in the blood vessel is at least 5 cm/s which is also required by claim 1. Answer,[4] page 4; page 5, lines 5-7.

[4] All citations to the Examiner's Answer are to the Answer mailed July 13, 2006. This replaced the defective Answer mailed March 30, 2006.

For the blood flow velocity limitation in claim 1, Nakano is cited for its teaching of an average velocity of 15.3 ±6.5 cm/s in the subjects who participated in their study. Id., page 8, lines 3-11. Thus, the Examiner presumes, "the blood flow velocity is at least 5 cm/s for subjects that experience myocardial problems." Id., page 8, lines 10-11.

The Examiner argues that the claimed requirement that the temperature difference be "above zero but not more than 0.39°C" to diagnose the presence of inflamed atherosclerotic plaque in the blood vessel would have been obvious in view of Casscells' '261 teaching "that an atherosclerotic plaque is present when the temperature elevation is about 0.2°C or greater." Answer, page 6.

Appellants contend that their invention resulted from the "realization" that when temperature measurements are made in the presence of blood flow at rates approaching or at physiological levels, "the temperature difference which is indicative of a vulnerable plaque can even be significantly lower than 0.39°C." Brief, page 12. They admit that "it was known before the invention was made that vulnerable atherosclerotic plaque exhibits a temperature which is elevated in comparison with 'normal' or non-inflamed vessel wall." Id., page 12. However, they urge that "[p]rior to the invention, studies had shown that the temperature, or thermal heterogeneity, exhibited by such vulnerable plaques, was generally at least 0.41°C above low-risk regions of the blood vessel." Id. "[M]issing from Casscells et al[.] is any teaching to the skilled reader that the temperature detected should be at the very low end of the range when the methods are carried out under conditions whereby blood flow is at least 5 cm/s." Id., page 14.

We do not agree with Appellants that the claimed temperature differential measured in a vessel with flowing blood is sufficient to impart patentability to the claimed method. As pointed out by the Examiner, Casscells '261 expressly states that the temperature of the vessel wall "can be measured with and without blood flow." Answer, page 6, lines 10-14; Casscells '261, column 30, lines 20-28. Casscells '261 also indicates that "continuous blood flow" can be maintained during temperature measurement. Id., column 31, lines 55-59. Casscells '261 actually measured vessel wall temperature in human arteriovenous grafts, non-invasively while blood was actively flowing through it. In this experiment, "[t]he inventors found that grafts are subcutaneous and superficial enough that their heat can be detected by an infrared camera." Id., column 38, lines 19-21. A graft with "good flow . . . revealed fine temperature heterogeneity." Id., column 38, lines 28-33. Non-invasive in vivo studies were also performed in rabbits in which temperature measurements were collected from an artery with intact blood flow. Id., column 35, lines 15-41. These disclosures make it clear that Appellants' characterization of "prior studies" as being performed in the absence of significant blood flow (Brief, page 12, § 4) is not a correct description of the cited Casscells '261 patent.

Appellants state that "[t]here is a suggestion at column 35 line 64 that an in vivo experiment was performed but it is not apparent that there was in this experiment any blood flow either." Brief, page 15, paragraph 2. Apparently, Appellants are referring to the experiment which in which temperature measurements were performed in a dog model of human atherosclerosis. Since these experiments are described as having been performed in vivo using devices "outside the animal's body to collect" temperature

measurements, our impression is that blood flow would have occurred inside the vessels. Casscells '261, column 36, lines 17-20. Nonetheless, immediately before the dog example, beginning on column 35, line 15, another experiment is described in rabbits in which temperature is measured in normal blood-filled vessels ("FIGS. 32A,B are color infrared photographs showing that in this Watanabe rabbit thermal heterogeneity is visible from the outside using an infrared camera. The rabbit's carotid arteries were momentarily retracted upward by sutures for photography." Id., column 35, lines 27-31.) Thus, we see no merit in Appellants' argument.

Nakano is cited by the Examiner to establish that, when experiments are performed on blood vessels through which blood flowed, the flow would have been at least 5 cm/s. Answer, page 8. Appellants do not challenge this finding, but instead argue that blood was significantly restricted under the conditions that Casscells '261 took vessel wall temperature measurements. Brief, page 14, ¶ 3. Having already rejected this argument, we agree with the Examiner's reasonable presumption that the blood flow velocity would have been "at least 5 cm/s" throughout Casscells' '261 method when conducted on vessels supplied with blood.

We now turn to the question of whether the claimed temperature range would have been obvious in view of Casscells '261. Appellants' range of "above zero but not more than 0.39°C" overlaps with Casscells' '261 preferred temperature range of "about 0.2 to 5°C." It is well-established that even a slight overlap in ranges establishes prima facie obviousness. See, e.g., In re Peterson, 315 F.3d 1325, 1329, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003). An exception has been recognized where a parameter had not been recognized as being a "result-effective variable." In re Antonie, 559 F.2d 618, 195

USPQ 6 (CCPA 1977). These circumstances are not present here because elevated temperature is identified by Casscells' 261 as the parameter which characterizes the presence of an inflamed atherosclerotic plaque. It was recognized by Casscells' 261 as a "result-effective variable." Accordingly, we conclude that the overlap in the temperature range between the prior art and the claimed subject matter is sufficient to establish prima facie obvious.

According to Appellants, "[t]here are general references in Casscells et al to temperature ranges from 0.2 to 5°C but it is quite clear that the focus in Casscells et al is on temperatures towards the middle of this range, especially 0.4 to 4°C and in particular 1.5°C and greater." Brief, page 14, ¶ 2. We do not find this argument persuasive. Casscells' '261 disclosure of higher temperature ranges (i.e., "especially 0.4 to 4°C and in particular 1.5°C and greater") cannot negate, or teach away from, his express disclosure of lower values that overlap with Appellants' claimed range.

In our view, the facts as discussed above clearly establish prima facie obviousness of the claimed subject matter, putting the burden on Appellants to set forth adequate evidence of secondary considerations. This burden has not been met. Accordingly, the rejection of claim 1 is affirmed. Because separate arguments for patentability were not made, claim 2-20, 22-25, 27-29, 34-41, and 43-50 fall together with claim 1.

Vacate and Remand

Claims 30-33

Claim 30 further requires "diagnosing the presence of inflamed atherosclerotic plaque in the blood vessel where the difference is above zero but not more than 0.14°C."

On consideration of the record before us, we conclude that the rejection of claims 30-33 as obvious over Casscells '261 in view of Nakano is not in condition for a decision on appeal. We vacate the rejection and remand the application to the Examiner to consider the following issues and take appropriate action.

1) Are claims 30-33 (or any other pending claims, including claim 1) inherently anticipated by Casscells '261?

Inherency asks whether a subject matter is "necessarily" present in the prior art reference, "not merely probably or possibly present, in the prior art." Trintec Indus. v. Top-U.S.A., 295 F.3d 1292, 1295, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002). It is the Examiner's burden to provide reason to believe that the claimed subject matter may be an inherent characteristic of the prior art. See In re Thrift, 298 F.3d 1357, 1365, 63 USPQ2d 2002, 2007 (Fed. Cir. 2002); In re Schreiber, 128 F.3d 1473, 1478, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997); In re Swinehart, 439 F.2d 210, 213, 169 USPQ 226, 228 (CCPA 1971). Once the Examiner has satisfied this duty, the burden shifts to Appellant to provide evidence to the contrary.

Claim 30 comprises the same steps recited in claim 1, which we have found (as discussed above) to be described by Casscells '261. The difference is that claim 30 diagnoses the plaque at a temperature "above zero but not more than 0.14°C." The

Examiner should determine whether Casscells ‘261 would have enabled temperature measurements to have been made within the claimed range, and if enabled, whether this is sufficient for the skilled worker to have reasonably believed that carrying out Casscells’ ‘261 method would necessarily result in the recordation of temperatures within the claimed range.

We note that, on the record before us, it is not evident whether Appellants have utilized a temperature detection device which enables them to measure temperatures lower than those recorded by Casscells ‘261. Appellants state that Casscells’ ‘261 value of 0.21°C “may have been chosen simply because it is apparently the limit of detection of the preferred apparatus.” Brief, page 15. However, this leaves open the question of whether other devices described by Casscells ‘261, or available prior to the instant application’s filing date, would have enabled temperature measurements in the claimed range to have been made.

Appellants argue that, when the detection method is carried out in the presence of blood flow, “the temperature difference which is indicative of a vulnerable plaque” can be significantly lower than 0.39°C. Brief, page 12. They explain that the reason for this difference is believed to be “due to the cooling or ‘smoothing’ effect of flowing blood in the vessel and that prior studies” were carried out with “absent or significantly reduced” blood flow, leading to “artificially high values.” Id. In other words, Appellants are not arguing that they improved the detection technology or enabled more sensitive measurements to be made, only that they discovered that the temperature of an inflamed plaque is lower when blood is flowing past it. Because Casscells ‘261, in fact, measures plaque temperature in several experiments when there is normal blood flow

through the vessel, the detection of plaque temperatures within the claimed range could be considered an inherent result[5] of carrying out the Casscells' method. threshold temperature and how this difference is reflected in the claimed subject matter.

2) Is there other prior art which would have enabled temperature measurements of inflamed plaques to be have been made within the claimed range?

If Casscells '261 would not have enabled temperature measurements to have been made in the claimed range, the Examiner should determine whether WO 01/742163, which is cited on page 7, lines 14-15 of the instant application as describing a preferred temperature measuring device, is prior art to the instant application. If so, the Examiner should consider whether there is adequate evidence to establish a prima facie case of obviousness over the combination of it and Casscells '261.

Additionally, we note that WO 01/742163 is pending as U.S. Application No. 10/169,523, which appears to have the same assignee as the instant application. The cited references in 10/169,523, particularly the references applied in the pending rejections, may also be combinable with Casscells '262 to establish prima facie obviousness of claims 30-33, or other pending claims in the instant application.

3) Is the instant application enabling under § 112, first paragraph, for diagnosing plaques at a temperature "above zero but not more than 0.14°C"?

In order to make a rejection under § 112, first paragraph, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for

[5] Because this reference is cited in the context of §103, we have not considered whether there is sufficient evidence to establish inherent anticipation under § 102.

the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In this context, the following issues should be considered:

First, Appellants state in their Brief (page 12), "during their investigations the inventors came to the important realization that when the methods are carried out in such a way that blood flows through the vessel at a significant rate (approaching or at physiological rates), in fact vulnerable plaques are indicated by temperature differences which are rather low, specifically not more than 0.39°C." Claim 30, however, is not limited to carrying out the method in the presence of blood flow. It is not clear from the record (and possibly inconsistent with it) that, when the method is carried out in the absence of blood flow, elevated temperatures in the claimed range would be experienced by inflamed plaques.

Second, it is not apparent whether the data presented in Tables 1 and 2 on pages 25-26 of the application, which show "results from patients . . . indicative of the likely presence of inflamed plaques," support the conclusion that the presence of inflamed plaques can be diagnosed where the temperature difference is "above zero but not more than 0.14°C" as required by claim 30. There is no information (e.g., number of measurements made in particular patient, standard deviation, etc.) to establish the significance of the data. For example, it is unclear on what basis Appellants have concluded that these values represent inflamed plaques rather than "biological noise" of the type described by Casscells '261. Column 23, lines 54-57. Similarly, patients 16 to 18 are described as "most at risk of plaque rupture." These patients show the highest amount of vessel temperature heterogeneity. In contrast, patients 5, 10, 13, and 14 exhibit about two-fold less heterogeneity. It is not evident how Appellants have ruled

out the smaller temperature deviations (e.g., 0.02, 0.03, 0.04, etc.) from being Casscells' biological noise.

It is also not apparent what the "lowest" and "highest" values in Tables 1 and 2 represent. The "lowest value" (reference) temperature is less than 0°C in 19 of the 21 patients. We assume that blood vessel temperature is not less than 0°C (or even just above 0°C); consequently, the listed values must represent something other than the vessel temperature, but it is not clear from the description what this is.

4) Is motivation to have improved the method of Casscells '261 provided by Casscells '075?[6]

According to Casscells '261, an estimated 35% of patients who have died suddenly from a heart attack have no active symptoms or diagnosis with coronary artery disease. Casscells '261, column 1, lines 37-42. Rupture of inflamed atherosclerotic plaques is an immediate cause of these heart attacks. Id., column 1, lines 45-47. Casscells '261 describes its method as useful for identifying the presence of inflamed plaques before they rupture, so that steps may be taken to avoid the occurrence of a potentially fatal cardiovascular event. Id., column 5, lines 39-44. The Examiner should consider whether normal desire of a physician to improve patient diagnosis and outcome in a fatal disease would have motivated him to extend the method's sensitivity to as low as possible, including values less than about 0.2°C, but above 0°C.

In the instant application, Appellants refer to Casscells' earlier work, including Casscells '075, for the teaching that elevated temperatures are associated with vulnerable plaques, particularly regions "described as being "0.4 to 2.2°C warmer."

[6] Casscells et al. (Casscells '075), U.S. Pat. No. 5,935,075, issued Aug. 10, 1999.

Specification, page 1, line 26-page 2, line 6. In the later filed patent, Casscells' 261 expands these results to a preferred range of about 0.2 to 5°C. In other words, it appears that Casscells was motivated to improve its own work, extending the method's sensitivity from a disclosed value of 0.4°C to a preferred value of about 0.2°C in the '261 patent.

Time Period

Regarding the affirmed rejection, 37 C.F.R. § 41.52(a)(1) provides "[a]ppellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner on remand.

This remand to the examiner pursuant to 37 C.F.R. § 41.50(a)(1) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)) is made for further consideration of a rejection. Accordingly, 37 C.F.R. § 41.50(a)(2) applies if a supplemental examiner's answer is written in response to this remand by the Board.

This application, by virtue of its "special" status, requires an immediate action. Manual of Patent Examining Procedure § 708.01. It is important that the Board be informed promptly of any action affecting the appeal in this case.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRM-IN-PART/VACATE-IN-PART AND REMAND

Donald E. Adams Administrative Patent Judge	)
	) BOARD OF PATENT
Nancy J. Linck Administrative Patent Judge	) APPEALS AND
	) INTERFERENCES
Richard M. Lebovitz Administrative Patent Judge	)

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